The Female Athlete Triad

A Clinical Guide

Catherine M. Gordon
Meryl S. LeBoff
Editors

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Preface

As will be discussed many times throughout this book, the Female Athlete Triad defines the interrelationship between menstrual dysfunction, low energy availability, and decreased bone mineral density. As is captured in several of the chapters, while some female athletes meet the psychiatric criteria for an eating disorder, others exhibit a milder energy deficit. However, all are at risk for premature bone loss and/or compromised attainment of peak bone mass. As co-editors, given our training and expertise in bone health across the age spectrum, we represent both providers of children, adolescents, and adults. It is important to recall that some skeletal health experts consider osteoporosis to be a "pediatric disease with geriatric consequences" given that the underpinnings of this disease occur during early to late adolescence [1]. This statement requires careful reflection when considering female athletes and the potential long-term health consequences. Physicians and health care professionals who see children and adolescents may have the opportunity to introduce strategies that augment peak bone mass, while providers of adults need to be cognizant of factors that occurred during childhood and adolescence that may compromise skeletal health during adulthood.

The organization of this book is geared towards clinicians who care for female athletes and researchers whose discoveries impact this important field, as well as translate back to clinical care. The book begins with insights on the epidemiology of the Triad and comments on the incidence of eating disorders among female athletes. Patients with these diagnoses represent the far end of the spectrum in terms of an energy deficit, which thus places them at high risk for health complications. While several of the chapters discuss bone health given our keen interest in this area as both clinicians and clinical investigators, we also try to provide an overview of other health complications. A chapter is devoted solely to stress fractures given how frequent this injury is among female athletes. Another complementary chapter discusses the musculoskeletal approach to the female athlete written from the vantage point of an orthopedic surgeon. Our authors come from a wide variety of disciplines which will hopefully broaden the applicability of the discussions captured herein. They include pediatric and adult endocrinologists, specialists in adolescent health and sports medicine, athletic trainers, gynecologists, orthopedic surgeons,

kinesiologists, dietitians, psychologists, and epidemiologists. Each of their perspectives is unique and important to consider as we think carefully about the complex issues that a female athlete faces.

We end the book outlining a research agenda and speculating on advances that will move this field forward and advance care for our patients. Challenges arise in understanding the most accurate way to evaluate bone health, both for the growing adolescent athlete, as well as for the active adult woman. New technologies are enabling us, for the first time, to catch a glimpse of bone structure and microarchitecture and assess skeletal strength as is discussed within this book. These new examinations are affording enhanced insight into fracture risk, the ultimate outcome of interest for athletes, for it is fractures that leave athletes sidelined and away from the activities they enjoy.

In closing, we wish to acknowledge and thank our wonderful families, whose support has made this book and all aspects of our work possible. Our husbands, Robert Bagley and Mark Williams; our parents, John and Sylvia Gordon and Gerald and Phyllis LeBoff; and last but not least, our children, Benny and Jack, and Jeremy and Avery. We gratefully dedicate this book to each of you.

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About the Editors

Drs. Catherine Gordon and Meryl S. LeBoff have been collaborators in the bone health field since 1994.

Dr. LeBoff, an adult endocrinologist, is the Chief of the Calcium and Bone Section in the Endocrinology, Diabetes and Hypertension Division in the Department of Medicine at Brigham and Women's Hospital (BWH). She founded and directs the Skeletal Health and Osteoporosis Center and Bone Density Unit in Endocrinology, Diabetes, and Hypertension Division. She is a Professor of Medicine at Harvard Medical School and the BWH, Distinguished Chair in Skeletal Health and Osteoporosis.

Working in close collaboration with Dr. LeBoff, Dr. Gordon, a pediatric endocrinologist and adolescent medicine specialist, founded the Bone Health Program at Boston Children's Hospital in 2000. Dr. Gordon is Director, Division of Adolescent Medicine at Hasbro Children's Hospital, and Professor and Vice-Chair for Clinical Research in the Department of Pediatrics, Warren J. Alpert Medical School of Brown University.

Drs. Gordon and LeBoff have collaborated on numerous studies in the area of skeletal losses in adolescents with anorexia nervosa and have received funding for their collaborative efforts from the National Institutes of Health, Department of Defense, and private foundations. Each is strongly committed to identifying factors that compromise bone health in adolescent girls and young women to optimize their acquisition of peak bone mass and skeletal health as adults. Their work encompasses the entire lifespan and represents a mission to understand ways to promote healthy bones and active lifestyles from young adulthood to older age.

Chapter 1
Definition and Epidemiology of the Female Athlete Triad

Emily Kroshus and S. Bryn Austin

Introduction

More women and girls than ever are participating in competitive sports [1]. In US high schools alone more than three million girls participate in interscholastic sports on an annual basis [2]. This is a largely positive development due to the many physical, mental, and social benefits of exercise, competition, and teamwork [3]. However, sport participation is not without health risks. In certain categories of sport, inadequate energy intake relative to energy expenditure, often out of a concern for weight and shape related to competitive and normative pressures, may put athletes at risk for the Female Athlete Triad. Sports typically classified as placing athletes at the greatest risk are those that are aesthetically judged (e.g., figure skating, artistic gymnastics, diving and synchronized swimming), have gravitational demands (e.g., distance running, cross-country skiing, cycling, and ski jumping) or in which there are weight classes (e.g., wrestling, boxing, judo, taekwondo, lightweight rowing, and weight lifting); we will refer to these as weight-sensitive sports [4].

The most recent position stand of the American College of Sports Medicine (ACSM) defines the Female Athlete Triad as resulting from the interrelationship among energy availability, menstrual function, and bone mineral density (BMD) [5].

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These three components of the Triad have been conceptualized as being on continua to reinforce the idea that graded negative health outcomes can occur at varying levels of each component; these continua range from optimal health on one end to pathology and disease on the other end. In 2014 the International Olympic Committee (IOC) released a consensus statement naming a new syndrome, Relative Energy Deficiency in Sport (RED-S) [6]. This syndrome highlights the role of energy deficiency in disrupting multiple dimensions of physiologic functioning (including but not limited to menstrual function and bone health) and is an extension of the concept of the Female Athlete Triad.

Energy Availability

Energy availability has been defined as the difference between daily dietary energy intake and exercise energy expenditure; daily calculations of energy availability are typically normalized to fat-free mass and expressed in kilocalories or kilojoules per kilogram of fat-free (or lean) mass [5]. The spectrum of energy availability ranges from high, meaning that the athlete consistently balances her dietary energy intake and energy expenditure, to low, where dietary energy intake is consistently less than exercise energy expenditure. For some athletes, low energy availability may occur because they have a clinically diagnosable eating disorder such as anorexia nervosa or bulimia nervosa [7]. However, individuals do not need to meet the diagnostic criteria for an eating disorder to be engaging in purging or restrictive behaviors that can alter metabolic and reproductive hormones and compromise BMD [5]. Individuals may be engaging in subclinical disordered eating behaviors, or they may be in an energy deficit due to other reasons such as not knowing how they should adjust their energy intake to compensate for an increased training load [8].

A gold standard measure of the construct of energy availability requires calculating energy expenditure through exercise and other physical activities and dietary intake, normalized for fat-free body mass. The recent position statement of the International Olympic Committee Medical Commission's Ad Hoc Research Working Group on Body Composition, Health and Performance [4] highlights the importance of considering issues of reliability, validity, and participant burden when selecting how to measure energy intake and energy expenditure. In addition to measuring energy intake and expenditure, these calculations require reliable and valid measures of body mass indices and body composition, accounting for factors such as hydration status [4]. Best-practice recommendations for assessing energy intake include recording intake on 3–7 training days and using multiple methods such as prospective dietary records and 24-h recall. Recommendations for assessing energy expenditures include accounting for the individual's energy expenditure at rest and completing (non-training) daily activities and training activities, with energy expenditure at rest ideally accounting for non-exercise adaptive thermogenesis or spontaneous physical activity.

If feasible, Sundgot-Borgen and colleagues [4] recommend using an objective method of assessment that does not rely on self-report, such as measuring oxygen consumption. Assessment of eating pathology using a validated measurement tool is one additional component of understanding whether an individual may be in energy imbalance, but should not be considered sufficient in isolation given the expanded conceptual definition of this component of the Triad [5]. Chapter 2 includes a detailed summary of "Sports Nutrition."

Menstrual Function

The spectrum of menstrual function has been defined as ranging from eumenorrhea to amenorrhea. Eumenorrhea is classified as having menstrual cycles lasting within one standard deviation of the mean length for young adult women (28 ± 7 days) [9]. Amenorrhea is classified by the absence of a menstrual cycle over a 3-month period [9]. Secondary amenorrhea refers to amenorrhea occurring after menarche, while primary amenorrhea refers to a delay in menarche past the age of 15 years [9]. On the spectrum between eumenorrhea and amenorrhea is oligomenorrhea, which is classified as having menstrual cycles lasting longer than one standard deviation past the mean cycle length for young women (>35 days).

Operationalization of the construct of menstrual function requires understanding current menstrual function and menstrual history, including age of menarche. Units of measurement are typically duration of menstrual cycles, calculated based on the self-reported number of menstrual cycles over a specified period of time. Stager et al. [10] have cautioned against the use of retrospective survey methods to assess age of menarche; however, this method may often be unavoidable without access to the individual's pediatric medical records, should these records even exist and be accurate with respect to menarche. Ideally, after pregnancy is excluded, measurement would include a draw of serum hormones to objectively assess estradiol and testosterone levels and to rule out other explanations for menstrual dysfunction, such as pituitary tumors and ovarian cysts [4]. Assessing whether or not respondents are taking some form of hormonal contraception is also a critical aspect of evaluation of menstrual function as hormonal contraceptives may regulate the presence of menses. Close to one-third of all sexually active US women who practice contraception use a hormonal method, such as a pill or vaginal ring containing estrogen and a progestin [11]. Additionally, female athletes with menstrual dysfunction are sometimes prescribed hormonal contraception based on conflicting evidence that this action may help maintenance of BMD, even though the balance of evidence weighs against its efficacy [12]. Consequently, if hormonal contraceptive use is not assessed, then any information about the frequency of menstrual cycles or the level of relevant hormones such as serum estradiol may reflect values that are exogenously maintained and independent of energy availability.

Bone Mineral Density

The spectrum of BMD refers to the range from optimal bone health to osteoporosis [5]. The National Institutes of Health Consensus Development Panel (2001) defines osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture." BMD is not the only component of bone strength, and fractures occur at different levels of BMD in different individuals. Nonetheless, BMD level is used in part to diagnose osteoporosis among young women, with a diagnosis of osteoporosis reflecting BMD below a level at which the risk of fracture is deemed "unacceptable" [5]. Previously, epidemiologic data from postmenopausal white women were used to predict risk of osteoporotic fracture from BMD in all populations. However this approach was criticized for not accurately representing age-specific risk in premenopausal populations [12]. The 2007 ACSM position statement [5] adopts the recommendation of the International Society for Clinical Densitometry (ISCD) [13] that BMD be expressed as a *Z*-score, with comparisons made to age- and sex-specific distributions of BMD. The 2007 ACSM position statement [5] defines osteoporosis as having BMD two or more standard deviations below the mean of the comparison group, along with other secondary clinical risk factors for bone fracture such as a history of nutritional deficiencies, hypoestrogenism or stress fractures. Since the release of the 2007 ACSM guidelines, the ISCD has released an updated position statement specifying that the terms "low bone mass or bone mineral density" rather than "osteoporosis" be used in the absence of history of clinically significant fractures [14]. Individuals can have compromised BMD without meeting the diagnostic criteria for osteoporosis; evidence of skeletal fragility must first be confirmed. Previously, the term "osteopenia" was used to refer to bone density measures that fall between a healthy BMD and osteoporosis. The most recent position statement of the ACSM [5] instead uses the term low BMD to refer to a bone density measure that is one to two standard deviations below the mean for age and sex, along with other secondary clinical risk factors for bone fracture. According to Sundgot-Borgen et al. [4] and the ISCD [14, 15], the gold standard method for measuring BMD is dual-energy X-ray Absorpiometry (DXA). The ISCD [14] states that the most appropriate skeletal sites for assessing BMD in children and adolescents tend to be the posterior-anterior spine and total body less head.

Prevalence

Estimates of the prevalence of the Female Athlete Triad or of individual components of the Triad have ranged from 1 % to over 50 % [16]. Reasons for this large range include variation in how components of the Triad are conceptualized and operationalized and differences in the age, sport, and level of competition of the populations sampled. The 2007 position statement of the ACSM on the Female Athlete Triad [5] provides the most commonly used conceptual definition for the components of the

Triad. Consequently, studies conducted prior to 2007 and using the previous iteration of the ACSM definition will necessarily be subject to misclassification according to the 2007 standard. For example, in 2007, ACSM replaced disordered eating with energy availability as one component of the Triad. Studies that measure eating pathology, but not energy availability, may misclassify individuals who are fueling themselves inadequately relative to their energy expenditure either inadvertently or intentionally, but do not report certain types of eating pathology [5].

Gibbs and colleagues [16] recently conducted a comprehensive review of the prevalence of the Female Athlete Triad, including the prevalence of its clinical and subclinical components, as reported in studies published between 1975 and 2011. We build on the work of Gibbs et al. [16] by using their search criteria and classification guidelines to update prevalence estimates. We include both studies that they review (1975–2011) and all English-language peer-reviewed papers published between January 2012 and 2014 assessing the prevalence of at least one Triad condition among premenopausal exercising women using self-report and/or objective measures. Included in the updated review are studies that report the prevalence of at least one clinical and/or subclinical disorder of the Triad. We draw particular attention to the small number of studies that have been conducted since the release of the 2007 ACSM Triad position stand using the updated conceptual definition for the Triad components, validated measurement tools, and reporting simultaneous prevalence of the three components of the Triad.

A total of ten studies published since 1975 have assessed the prevalence of all three components of the Triad [16, 17], with prevalence estimates for all three components ranging from 0 % in a sample of 82 physically active females (mean age 31 years, standard deviation (SD) = 7) [18], and 0 % in a sample of 15 women on a club triathlon team (mean age = 35, SD = 6) [19] to 15.9 % in a sample of 44 elite female endurance athletes [20]. However, only four studies assessing prevalence of all three Triad components have been conducted since the 2007 ACSM update [17, 19–21], and even then they did not all operationalize the constructs of the Triad according to the 2007 ACSM standard (see Table 1.1). One of these four studies, conducted by Schtscherbyna et al. [21] in a sample of 78 elite female swimmers (mean age = 14.6 years, SD = 2.0 years), did not incorporate the concept of energy availability into the measurement of prevalence, assessing only disordered eating using three validated written measures of disordered eating risk. Nearly half (44.9 %) of the sample met the threshold set by the authors for disordered eating for at least one of three self-report measures of eating pathology (Eating Attitudes Test [EAT-26], Bulimia Investigatory Test Edinburgh [BITE], Body Shape Questionnaire [BSQ]). No athletes were classified as having primary or secondary amenorrhea, and 19.2 % were classified as having oligomenorrhea. Athletes using hormonal contraceptives were excluded from the study; however, no information was given about the number of individuals excluded based on this criteria. Low BMD, as measured using DXA and classified by a *Z*-score of below −1, was present in 15.4 % of the athletes. According to this study's operationalization of Triad, 15.4 % of the sample had clinical levels of at least two components of the Triad, and 1.3 % meet criteria for all three components.

Table 1.1 Characteristics of the studies published after 2007 of the prevalence of all three components of the Female Athlete Triad

Study	Sample	Energy availability: measurement (EA)	Energy availability: prevalence (%)	Menstrual function: measure	Menstrual function: prevalence (%)	Bone mineral density: measurement (BMD *Z*-score)	Bone mineral density: prevalence (%)	Three-way prevalence[a]
Hoch et al. (2009)	Sport: High school varsity sports (all teams)	EA ≤ 45 kcal/kg LBM	36	Primary amenorrhea, secondary amenorrhea or oligomenorrhea	54	$-1.9 < z \leq -1.0$	13	1.0 %
	Mean age: 16.5 years, SD = 1.0, *n*: 8	EA ≤ 30 kcal/kg LBM	6					
	Country: USA	EAT-26 ≥ 15	4	Secondary amenorrhea	30	$z \leq -2.0$	3	
Schtscherbyna et al. (2009)	Sport: Swimming	EA	Not measured	Primary or secondary amenorrhea	0	$z \leq -1.0$	15.4	1.3 %
	Mean age: 14.6, SD = 2.0, *n*: 8	Positive screen for one of three self-report measures (EAT-26, BITE or BSQ)	44.9	Oligomenorrhea	19.2			
	Country: Brazil							
Pollock et al. (2010)	Sport: Endurance running	EA	Not measured	Secondary amenorrhea or oligomenorrhea	52.3	$-1.9 < z \leq -1.0$	4.9–34.2	15.9 %
	Mean age: 22.9, SD = 6.0, *n*: 44	Upper quartile on any of the three subscales	Not reported			$z \leq 2.0$	0–33.3	
	Country: UK							
Coehla et al. (2013)	Sport: Tennis	Stage I: EA ≤ 45 kcal/kg LBM	87.5	Stage I = primary amenorrhea, secondary amenorrhea or oligomenorrhea	33.3	Stage I: $z \leq -1.0$	25.0	Stage I: 4.2 %
	Mean age: 14.8, SD = 10.6, *n*: 24	EA ≤ 30 kcal/kg LBM	33.3	Stage II = primary amenorrhea or secondary amenorrhea	8.3	Stage II: $z \leq -2.0$	0	Stage II: 0 %
	Country: Brazil	Stage II: EAT-26 > 20 or BSQ > 80 or BITE > 10	50.0					

EAT-26 Eating Attitudes Test-26 score, *BITE* Bulimic Inventory Test Edinburgh score, *BSQ* Body Shape Questionnaire score, *TFEQ* Three Factor Eating Questionnaire score, *DXA* Dual X-Ray Absorptiometry, *LBM* lean body mass

[a]Three-way prevalence refers to simultaneous prevalence of all three components of the Triad

In line with the updated definition, Hoch et al. [19] assessed the prevalence of all three Triad components in a sample of 80 female high school varsity athletes across multiple sports. Around one third (36 %) of the athletes were classified as having low daily energy availability (≤45 kcal/kg of lean body mass), with 6 % having energy availability of less than 30 kcal/kg of lean body mass. In addition to the gold standard of energy availability, eating pathology was also measured, with only 4 % of athletes classified as at risk of disordered eating based on having EAT-26 scores of greater than or equal to 15. Over half of athletes (54 %) reported menstrual dysfunction, with 30 % reporting secondary amenorrhea and 15 % reporting oligomenorrhea, both operationalized using the 2007 ACSM definition [5]. Hormonal contraception was assessed and reported, but results were not stratified by use. Serum hormones were also assessed to eliminate other endocrinologic or gynecologic causes of menstrual dysfunction. BMD was assessed using the 2007 ACSM [5] definitions and using DXA technology: 3 % of athletes had *Z*-scores of less than −2, and 13 % had *Z*-scores between −1 and −1.9. Overall, the authors found that 1 % of the sample had all three Triad conditions, between 4 and 18 % had any two Triad conditions, and between 16 and 54 % had any one Triad condition.

Pollock et al. [20] assessed the prevalence of the conditions of the Triad in a sample of 44 elite female endurance runners (mean age 22.9 years, SD = 6.0 years). BMD was measured at several locations on the body, with *Z*-scores varying by location. Low BMD, as measured by *Z*-scores of between −1 and −2, was characteristic of 34.2 % of the sample at the lumbar spine, 13.8 % at the femoral neck, 29.6 % at the radius, and 4.9 % for the total body. *Z*-scores below −2 were characteristic of 7.3 % of the sample at the lumbar spine, 33.3 % at the radius, and 0 % at the femoral neck and for the total body. Energy availability was not assessed. Rather, disordered eating was assessed using the Three-Factor Eating Questionnaire (TFEQ), a self-report measure of disordered eating cognitions, including cognitive restraint. Athletes scoring in the upper quartile for this sample on any of the three TFEQ subscales were classified as engaging in disordered eating. Secondary amenorrhea or oligomenorrhea, assessed using a self-report questionnaire, were present in 52.3 % of the sample. While information on hormonal contraceptive use was reported, results were not stratified by its use. Considering the sample as a whole, 15.9 % were classified as having all three components of the Triad, with menstrual dysfunction, disordered eating and low BMD.

Coehla et al. [17] also used the 2007 Triad definition to assess prevalence of the Triad in a sample of 24 adolescent female tennis players. Although the participants were from only one sport and the sample size was small—thus producing imprecise estimates with wide confidence intervals—this study is notable because it is the first and only study to date to estimate the prevalence of the Triad using the spectrum concept. The authors divided the Triad into Stage I and Stage II to reflect graded severity. Stage I was considered to be "moderately severe" and was operationally defined as having daily energy intake of less than or equal to 45 kcal/kg of lean body mass, presence of primary or secondary amenorrhea or oligomenorrhea, and a BMD *Z*-score of less than or equal to −1.0. Stage II was considered to be "severe" and was operationally defined as meeting a clinical threshold for at least one of three

validated self-report measures of disordered eating (Eating Attitudes Test-26 > 20, BSQ > 80, Bulimic Investigatory Test Edinburgh > 10), presence of amenorrhea, and a BMD *Z*-score less than or equal to −2.0. Of note is that building from the ACSM's definition, a gold standard measure of a "severe" classification should include having daily energy intake ≤30 kcal/kg of lean body mass and not solely the presence of eating pathology [5]. Nonetheless, using these definitions, 4.2 % of the athletes met criteria for all three components of Stage I of the Triad, with 5.0 % having low energy availability, 33.3 % having menstrual irregularity, and 25.0 % falling one or more standard deviations below the age- and sex-adjusted mean. No athletes in this sample met criteria for all three components of Stage II of the Triad, with 50 % meeting criteria for disordered eating, 8.3 % classified as amenorrheic, and 0 % having BMD *Z*-score ≤ −2.0. There may be disagreement about whether a two-stage approach and the choice of measures and thresholds at each stage in this study were most appropriate to represent the spectrum of risk; however, this study represents an important starting point for the design of future studies to assess the prevalence and severity of the Female Athlete Triad.

Since the 2007 update of the ACSM definition of the Triad to encompass a spectrum of energy availability, with or without disordered eating, few studies have assessed the prevalence of energy availability among female athletes using validated methods. In addition to the work of Coelho et al. [17] and Hoch et al. [19] as described above, Reed et al. [22] and Da Costa et al. [23] measured energy availability among female athletes. In a sample of 77 adolescent swimmers (age 11–19 years), Da Costa and colleagues found 16 (20.8 %) to have daily energy availability below 45 kcal/kg of lean body mass, and 6.5 % had daily energy availability below 30 kcal/kg of lean body mass [23]. In a rare longitudinal study, Reed et al. [22] measured how energy availability varied across the competitive season on a team of 19 female collegiate soccer players. The percentage of players with daily energy availability below 30 kcal/kg of lean body mass was 26.3 % pre-season, 33.3 % mid-season, and 11.8 % post-season. The authors found this difference to be driven by lower dietary energy intake at lunch and dinner during mid-season as compared to other points in the season.

Because most studies available on the prevalence of the Triad (and components of the Triad) were published prior to the 2007 ACSM definition update, many more studies report the prevalence of disordered eating than energy availability. In the studies reviewed by Gibbs et al. [16], disordered eating and eating disorders were assessed using structured clinical interviews or validated survey measures that measure eating pathology or risk factors for eating pathology. In summary, 35 studies of the prevalence of clinical or subclinical disordered eating or eating disorders were either included in the review of Gibbs et al. [16], or were published later and met their inclusion criteria. The prevalence of subclinical disordered eating among all exercising women included in the studies reviewed ranged from 2.9 to 60 % [4, 16]. The prevalence of clinical disordered eating, such having an EAT-26 score of ≥20, ranged from 7.1 to 89.2 % [16, 17, 23]. Estimates of the prevalence of clinical eating disorders ranged from 0.9 to 40.8 % for bulimia nervosa and from 0 to 48.0 % for

anorexia nervosa [16, 24]. While these rates of eating disorders and disordered eating suggest that eating pathology, and likely inadequate energy intake, may be endemic in certain populations of female athletes, they do not provide concrete information about energy availability according to the 2007 ACSM standards.

Considering all studies published between 1975 and 2011 that were reviewed by Gibbs et al. [16] and between 2011 and 2013 using the same criteria for study inclusion, prevalence of secondary functional hypothalamic amenorrhea ranged from 1 to 60 % [16, 17, 25, 26]. The prevalence of oligomenorrhea ranged from 0.9 to 52.5 % [16, 26–29]. The prevalence of primary amenorrhea ranged from 0 to 56.0 % [16, 17] with the highest prevalence recalled by adult professional ballet dancers in the USA and Western Europe. Subclinical menstrual irregularity was assessed using hormonal measures in four studies, with prevalence ranging from 5.9 to 43.0 % [16]. Of note is that analyses were not stratified for hormonal contraceptive use; when hormonal contraceptive use was measured, it is typically either reported as a descriptive statistic or used as exclusion criteria.

Considering studies that used the 2007 ACSM and 2014 ISCD definitions of low BMD, estimates of the prevalence of subclinical low BMD in female athletes ranges from 0 to 40 % [15, 16], and the prevalence of clinical low BMD from 0 to 15 % [16, 17].

Males

While the focus of this book is on female athletes, it is important to consider similar issues that arise in the athletic male. Like female athletes, when male athletes experience chronic low energy availability, they are at risk of hormonal disruptions that can negatively influence BMD [30, 31]. Male athletes participating in weight-sensitive sports are more likely to have low BMD [32]. Volume of endurance training, a measure of energy expenditure, has been associated with lower BMD [33, 34] and lower levels of serum testosterone and gonadal hormones [35, 36]. Additional research is needed to explicate more fully a definition for the Male Athlete Triad and to document the prevalence of this interrelated triad of disorders in male athletes. Presently, most studies of males involve small samples of 10–15 athletes. Including studies with larger samples is necessary for estimating prevalence with a reasonable degree of precision.

Conclusions

Few studies with female athletes exploring the prevalence of the Triad have operationalized its components using the 2007 ACSM definitions nor have they represented the spectrum of risk in the estimates reported. Future research on the

prevalence of the Triad is warranted and ideally should meet the following criteria: (1) Triad components should be conceptualized using the 2007 ACSM and 2014 ISCD definitions; (2) energy availability should be adjusted for fat-free mass and assessed using an objective method, such as oxygen consumption, or using a validated method of assessing dietary intake and energy expenditure, measuring multiple days and accounting for energy expended at rest, non-training physical activity and athletic training; (3) assessment of menstrual function should include, at a minimum, age at menarche, menstrual function over the previous 3 months and hormonal contraceptive use, with estimates stratified by its use; (4) BMD should include a measurement from DXA and be reported using *Z*-scores relative to age- and sex-specific standards; (5) for all reports of prevalence, the age, sport, and competitive level of the population should be specified, with the sport or group of sports classified as weight-sensitive or not weight-sensitive, as appropriate; and (6) sample sizes should be sufficiently large to produce reasonably precise prevalence estimates for rare outcomes, with confidence intervals around all estimates reported. At the present time, estimating prevalence of the Triad with a reasonable degree of validity and precision is difficult because of the varying ways in which the Triad and its components have been conceptualized and operationalized. By following the criteria outlined above, validity and precision of estimates of the prevalence of the Triad will be strengthened. Accurately estimating the prevalence of the Female Athlete Triad and its counterpart in male athletes will be critical for informing prevention efforts and monitoring population-level changes in risk over time.

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Chapter 2
Sports Nutrition

Katrina Schroeder and Kendrin R. Sonneville

Introduction

There are a many articles written about the female athlete triad including studies on bone health, hormone regulation, eating disorders, and excessive exercise. These studies consistently conclude that eating a balanced diet appropriate for the level of physical activity can resolve the problem, in other words fixing the "energy availability" component of the triangle. Proper nutrition may not add years back to bone age or health for an adolescent girl or make up for months or years of amenorrhea, but with sufficient energy intake, periods should resume, hormones should come back into balance, and bones should begin to strengthen. Undoubtedly, sports nutrition is an essential component of the prevention of, the prescription for management of, and the continued care for treatment of the female athlete triad.

The macronutrients protein, carbohydrate, and fat make up any healthy diet. A sports diet needs appropriate quantities of each component: carbohydrate to fuel the body, protein to rebuild, and fat to absorb nutrients and prevent disease. Someone who eats a healthy, balanced diet should not need to make major dietary changes to have a healthy, balanced, "sports diet." As the position paper of the Academy of Nutrition and Dietetics, Dietitians of Canada, and American College of Sports

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Medicine states, "the fundamental differences between an athlete's diet and that of the general population are that athletes require additional fluid to cover sweat losses and additional energy to fuel physical activity" [1].

Micronutrients are also extremely important for an athlete. Specifically for active women, iron, calcium, and vitamin D must be provided in appropriate quantities to prevent injury and other negative outcomes associated with sport such as fatigue and stress fracture. While this chapter focuses on sports nutrition including what to eat pre-, during, and post-workout, it is important to emphasize that a healthy, varied, balanced diet will provide these important nutrients and does not need to change substantially or include expensive supplements in its makeup to become a "sports diet." However, there are certain percentages of nutrients, timing tips, and other tools that individuals can use to modify their diet to improve athletic performance. Whether modifying an athlete's diet is needed to address a problem such as the female athlete triad or if it is the focus of a performance improvement plan, ensuring that enough energy is consumed consistently is essential.

As the other chapters of this book have shown, an energy deficit, whether inadvertent or intentional, can cause serious harm. Despite the popular belief that athletes can eat whatever they want because they burn many calories through training, the foods they eat must be varied enough to ensure that correct amounts of vital nutrients are being consumed. One might think that after a vigorous bout of exercise, an athlete would be especially hungry, so that if she does not adequately refuel, then it must be intentional (i.e., for weight loss or due to body image issues). However, recent studies of appetite-related hormones in female athletes have shown that exercising can raise the levels of peptide YY and ghrelin, resulting in a suppressed appetite rather than an appropriate level of hunger necessary to fuel the body [2]. Sometimes athletes need a reminder that they must refuel, whether their body is sending them the correct signals to do so or not.

Dietary Assessment

Assessing an athlete's diet requires asking numerous questions. A 24-hour food recall is generally a good place to start. However, the past 24-hour intake may not adequately capture the typical intake of an athlete whose diet varies substantially from day to day because of training demands. When assessing an athlete, it is better to be more specific and ask for a dietary recall for a practice day, game day, and rest day, for example. Some athletes will fuel appropriately during training, but get an upset stomach prior to competition and will eat or drink very little out of fear that needing to use the bathroom during competition will affect their performance. Others may eat adequately on days when they exercise, but skimp on days that they know that they will not be "burning it off" at the gym. In assessing an athlete's diet, a clinician can begin to see trends: Do they avoid meat or grains? Are they getting enough dietary fat? Are they restricting calories or overloading on protein? In addition to food and beverages, it is also important to ask about any vitamins, supplements, or other ergogenic aids such as caffeine that they may be taking.

In addition to diet, it is important to ask about hours and intensity of activity each day. As you will see, that is one factor in assessing caloric needs. However, another important reason for asking is because not all women who exercise consider themselves "athletes" or think that they would fit the category of needing a sports diet. Lack of recognition of intensity of exercise could prevent someone from getting the extra nutrients that they need.

It is beneficial to conduct an anthropometric assessment of athletes and, depending on the athletes and their needs, to measure body composition in the assessment. The standard assessment is the body mass index (BMI) which is a measurement of a person's height in relation to her weight (kg/m^2). Although BMI only takes into account height and weight, there is a good correlation between BMI and % body fat among adults [3]. Because the BMI is an indirect measure, which cannot discriminate between lean mass, fat mass, and bone, it may be less accurate for use among athletes with higher muscle mass and lower body fat percentage than the general population [4]. However, BMI assessment is a useful tool when included as part of a complete assessment of an athlete's health, especially for those who are underweight or at risk for an eating disorder. As an example, an individual's BMI or the trend in her BMI, especially during adolescence, may be more revealing than her report of amount of activity and quantities of food consumed.

If more detailed information about an athlete's body composition is desired, body fat percentage can be estimated by using calipers to measure the thickness of subcutaneous fat in multiple places on the body including the abdominal area, the subscapular region, arms, buttocks, and thighs. Alternatively, a more accurate and precise method of measuring body composition is by dual X-ray absorptiometry (DXA), which makes it possible to determine the amount of total and regional fat and lean tissue including the fat and lean mass indices normalized to height squared. Alternatively, bioelectrical impedance analysis or air displacement plethysmography (Bod Pod®) can be used, although each requires equipment that is not commonly available. Once the data have been gathered, it is important to know what goals an athlete has. Is she looking to gain muscle, lose fat, or reach a specific weight in order to compete at a certain weight class? Is she attempting to reach an unrealistic body fat percentage? The goal will help to guide the nutritional counseling, ensuring that whatever the athlete's goals, she is attempting to reach them in a safe and healthy way.

Energy Requirements

Energy requirements for athletes vary substantially from sport to sport. Athletes in certain sports such as wrestling, boxing, or rowing may need to maintain a specific weight in order to compete; others may strive for a certain body ideal for sports like dance or gymnastics. Still others such as distance runners, cyclists, or swimmers may be burning so many calories in their training that they find themselves in negative energy balance without even realizing it.

The easiest method for determining an athlete's total daily energy needs is to use the Harris Benedict Equation (see below) because all that must be known is the athlete's weight, height, and age.

Harris Benedict Equation

$$\text{Females}: \text{Resting metabolic rate}\left(\text{RMR}\right) = 665.0955 + 9.5634 \times \text{Weight in kg} + 1.8495 \times \text{Height in cm} - 4.6756 \times \text{Age in years}$$

Direct estimates of energy requirements, such as indirect calorimetry, require the use of costly equipment and other methods of calculating energy requirements require knowledge of an athlete's lean body mass (determined through the methods described above). For example, RMR can be estimated using the Cunningham Equation (below), although fat-free mass must be known in order to calculate.

Cunningham Equation

$$\text{Females}: \text{Resting metabolic rate}\left(\text{RMR}\right) = 370 + 21.6 \times \text{Free} - \text{Fat Mass}$$

The RMR, found using either method described above, indicates the amount of calories burned at rest; multiply this by an activity factor of 1.8–2.3 depending on activity level to account for calories burned above and beyond the RMR. An activity level of 1.8 would equate to someone who exercises around an hour each day whereas 2.3 would be someone who is exercising for several hours each day [4].

Macronutrients

Carbohydrate

Carbohydrates should be the foundation of any healthy meal plan, especially that of an athlete. An athlete should consume from 6 to 10 g/kg/day of carbohydrate, depending on activity level and type of activity [1]. For someone exercising 1 h/day, the lower end of this range would suffice, but athletes exercising intensely, possibly even more than once a day, should aim for the higher end of the range. Intake of carbohydrates should be spread fairly evenly throughout the day rather than included only in one big meal, for example, at dinner [4].

Carbohydrates are found in different places in the body: stored in the muscles as glycogen, stored in the liver as glycogen, and circulating in the blood as glucose [4]. Athletes need to consume enough carbohydrate so that their glycogen stores are

maximized and ready when they begin exercise. The body uses carbohydrates to fuel exercise; half of the energy for moderate-intensity exercise comes from muscle glycogen and blood glucose and two thirds of the energy for high-intensity exercise does [4]. Athletes need to replace these stores during exercise lasting longer than 1 h in duration with food and/or drink that contain carbohydrates in order to have continued fuel. It is important to note that no amount of eating or drinking during exercise can make up for beginning with depleted stores [5].

Adequate carbohydrate intake is not only important for endurance athletes such as runners or cyclists who might generally hear advice about *carbo loading*. Athletes on team sports or those who compete in shorter distance activities will also need stored energy for practices and will need adequate fuel available for the short bursts of energy necessary during competition. Officially, *carbo loading* is more than just eating a pasta dinner the night before a race or athletic event, although some athletes may still do this as a last ditch effort to top off glycogen stores. As stated previously, anyone participating in athletics should make sure to get enough carbohydrates in their diet on a consistent basis. The theory behind *carbo loading* is that athletes can maximize their glycogen stores by eating the low end of the recommended amount of carbohydrate starting 6 days prior to the competition or event. They continue with this for 3 days at which point they increase to the high end of the recommended amount of carbohydrate for the final 3 days leading up to the competition [5].

There are negative consequences associated with inadequate muscle glycogen stores, as well as inadequate liver glycogen stores. When muscle glycogen is too low and not repleted, athletes may "hit the wall" and find that they can no longer continue at the same level of performance as they could previously. This tends to happen more during endurance activities such as a long-distance running event or cross-country ski race. Liver glycogen and blood sugar provide fuel for the brain; when there is not enough an athlete may lose motivation to continue performing or become disoriented despite the availability of the muscle stores to continue—sometimes this is referred to as "bonking" [6]. This is why it is important not only to eat carbohydrates consistently on a daily basis (and possibly also *carbo load* leading up to an event), but also to eat a source of carbohydrate in the hours immediately prior to the event.

There are many food and beverage sources of carbohydrate from one or more of the following categories: fruit, vegetables, grains, dairy, beans, nuts, and sugar. Some of these carbohydrate sources are healthier than others. Accordingly, the U.S. government's MyPlate recommendations suggest that half of all grains consumed should be whole grains such as whole wheat, whole wheat pasta, brown rice, quinoa, oats, bulgur, barley, and amaranth in order to help prevent heart disease and ensure adequate fiber intake. In addition, not all carbohydrates perform the same once they have been eaten. The speed and amount which a certain food raises a person's blood sugar is referred to as the glycemic index (GI). A low GI food will slowly raise blood sugar and slowly bring it back down. A high GI food will spike blood sugar quickly and can bring it down fast as well. The blood sugar response to a particular food depends on the makeup of the food as well as what it is eaten in concert with. Generally speaking, a low GI food such as a banana or

glass of milk might better serve an athlete prior to exercise whereas a high glycemic index food like gummy bears or juice might better serve an athlete during or immediately after exercise [6].

Protein

The RDA for protein intake for a healthy adult is 0.8 g/kg/day and the "Acceptable Macronutrient Distribution Range" is 10–35 % of daily calories provided by protein. For endurance athletes, that amount can increase to 1.2–1.4 g/kg/day and the amount can go even higher for strength training athletes, up to 1.7 g/kg/day. Some athletes may think that they need to take in excess amounts of protein in order to build muscle. However, it is a combination of total energy intake with sufficient protein and resistance exercise that build muscle, not excessive protein intake. Athletes interested in building muscle must eat appropriate amounts of "protein-sparing" carbohydrate in order for the essential amino acids to remain free to build muscle [1]. There is also the opposite risk of having too little protein which can cause the breakdown of muscle, a side effect any athlete will want to avoid [5].

While it is entirely possible for an athlete to meet her protein requirements by eating a varied diet that includes protein sources such as meat, fish, poultry, tofu, beans, legumes, nuts, and dairy, some turn to protein powders or bars. An athlete can find protein powder in all sorts of varieties: from standard whey or soy protein to egg white and beef protein to vegan pea, hemp, and rice protein (notice that all of these protein powders originate from food sources). If she finds it convenient and cost effective to consume protein in powder form, it is not necessarily detrimental (although a thorough review of other ingredients is important) but it is not necessary either. Regardless of the source or form, protein still contains 4 cal/g. An athlete should be aware of not just the grams of protein she is consuming, but also the potential for extra calories in an extremely high-protein diet. Also, many protein powders are flavored with artificial sweeteners in order to reduce the calories in the powder but keep the taste acceptable. Athletes who might be sensitive to artificial sweeteners, such as those with irritable bowel syndrome, should be sure to read label and ingredient list on protein powders carefully.

When a person consumes excessive amounts of protein, she risks becoming dehydrated due to the increased urine that is created as the body disposes of the excess ammonia derived from amino acids. This is called nitrogenous waste and is created by the liver once the kidney has worked to filter out the excess nitrogen [5].

Fat

The percentage of fat in an athlete's daily diet should be between 20 and 35 %. Less than this amount may have an adverse affect on performance and can hinder a person's ability to absorb fat-soluble vitamins (A, D, E, and K). Eating a diet higher in fat than 35 %, however, does not appear to be beneficial to athletes [1, 4].

Athletes who need to consume large amounts of calories each day to avoid an energy deficit should utilize fat source not just for its health benefits but also due to its energy density. Fat contains 9 cal/g as opposed to carbohydrates and protein both of which contain 4 cal/g. However, emphasis should be placed on unsaturated fats which are derived from plant sources such as avocado and nuts rather than saturated fats which are derived from animal sources such as butter and cream.

For low-intensity exercise (and when a body is at rest), fat stored in the body is used as a source of fuel. As exercise intensity increases, the body more efficiently uses carbohydrate more so than fat as the fuel source [5]. Some athletes may ask about using medium chain triglycerides (MCTs) as an alternative energy source to carbohydrates. MCT oil is marketed to athletes as a way to boost energy and maximize performance, although research studies have found little benefit related to its use. Instead, MCT has actually been shown to cause gastrointestinal distress and elevated blood lipid levels [4]. Another type of fat advertised to athletes is branch-chain amino acids (BCAAs) made up of leucine, isoleucine, and valine. These have also shown no improvement in performance, though they may have a benefit related to immune function [4].

Pre-, During, and Post-workout Fueling

Pre-workout

Athletes will perform better if they are adequately fueled prior to performance [1]. What a person eats prior to practice or competition will depend partly on how much time is available. Having a meal 3–4 h prior to activity and a small snack 1 h before can give the body time to digest but remain fueled, which is realistic for activities that occur later on in the day. If an athlete will be practicing or competing in the early morning, she may not have enough time to eat anything substantial between waking up and exercising. In this case, a small meal prior to bed the night before might be the best way to ensure that her body is ready for activity upon waking [6]. Ideally, she will wake up at least an hour before activity so that she can eat a small meal and digest before beginning exercise.

While many have sought the "perfect" pre-race meal, it will likely differ from individual to individual based on foods that they best tolerate. The meal or snack should be consumed with enough time to digest it, should leave the athlete feeling satiated, should be low in fat and fiber so as not to cause an upset stomach, should be high in carbohydrate to give energy, and should be moderate in protein [1]. This combination may sound overly specific and possibly even unattainable, but there are easy ways to achieve this. For example, a piece of white bread with a small amount of peanut butter or an English muffin with a slice of cheese and an egg white would meet these requirements, as would some trail mix and a glass of orange juice. The pre-race or pre-workout meal does not need to come in a package and does not need to be sold for that specific purpose; often the normal foods that one eats, perhaps with slight modifications to portion size and makeup, can be just the right pre-workout meal or snack.

Here are some other suggestions for healthy pre-race meals or snacks (portions depend on timing and intensity of workout, and on the individual athlete):

- Peanut butter and banana in a whole wheat wrap
- Turkey sandwich with a glass of orange juice
- Bagel with cream cheese
- Energy bar with an apple
- Pita chips or pretzels with hummus
- Baked potato with cottage cheese and broccoli

During Workout

Consuming carbohydrates during exercise, mainly in the form of glucose, can enhance performance when exercise will last longer than 60 min [1]. It is important that whatever is ingested during activity has been tested by the athlete prior to competition and is known to be well tolerated. Popular products such as gels and chews can provide the necessary fuel and will be quickly digested and absorbed by the body. If exercise will last longer than 60 min, ingesting carbohydrates at the rate of 0.7 g/kg body weight per hour can extend performance [1]. For a 130-lb athlete, this would equal around 41 g of carbohydrate per hour or the equivalent of two energy gels. A small banana and 12 oz of Gatorade would also provide enough carbohydrates for that athlete.

Post-workout

After exercise, it is necessary to restore depleted glycogen stores with carbohydrates as well as rebuild broken-down muscle with protein. There have been a few different reported "ideal" ratios of carbohydrates to protein for post-workout such as 3–1 or 4–1. These ratios may surprise athletes who think that they need to focus primarily on protein for recovery [6]. Chocolate milk is a favorite recovery beverage among many endurance athletes due to the combination of carbohydrate and protein, not to mention the electrolytes that are found naturally in milk such as sodium and potassium [6]. Despite the fact that this simple beverage or other whole foods can provide all of the carbohydrates and protein necessary for a post-workout snack, many athletes believe that they need to consume excess amounts of protein and are prone to believe marketing campaigns and internet postings leading them to recovery shakes, protein powders, and other products that may contain unnecessary nutrients, untested supplements, and chemicals that could harm the body in the long run.

Refueling within 30 min of a workout can restore glycogen faster, but depending on the length and intensity of the workout, it may not be necessary to worry about the timing as long as a meal with carbohydrates and protein will be consumed within

2 h. With the increased amount of carbohydrates that an athlete should consume, a post-workout snack should be eaten if a meal is not imminent [1].

Micronutrients

Iron

Women need more iron than men to begin with due to the blood loss that occurs during menstruation and are at higher risk for iron deficiency anemia. The Dietary Reference Intakes (DRIs) put out by the Institute of Medicine recommend that females ages 9–13 consume 8 mg of iron per day. Those ages 14–18 should consume 15 mg/day and from 19 to 50 should consume 18 mg/day. Over age 50, the recommendation decreases back down to 8 mg/day [7]. However, endurance athletes need as much as 70 % more iron than their non-athletic counterparts [1]. Iron deficiency anemia can be especially detrimental for athletes who could suffer performance setbacks due to the symptoms of anemia such as fatigue and decreased motivation.

Vegetarians and vegans should pay especially close attention to their iron intake (see "Special Populations" section below). Women who may not identify as vegetarian, but who may avoid red meat due to the perception that it is unhealthy, are also a population at risk of inadequate iron intake. While avoiding red meat can be a healthy dietary choice, it can also be included as part of a healthy, balanced diet by choosing lean cuts, trimming any excess fat, and limiting consumption to two to three times per week. It is possible that while not technically a vegetarian, she may not be consuming much meat but also not meeting her iron needs via plant-based sources. Iron supplements are an option but can have negative side effects such as gastrointestinal distress. If possible, encourage athletes to analyze how much iron is in their diet and to increase the amount, whether plant based or animal based.

Vitamin C plays a supporting role in iron absorption. As such, athletes should have a source of vitamin C each time they are consuming an iron-containing food. This could be a glass of orange juice alongside iron-fortified cereal, green peppers sautéed with chicken, or tomatoes added to bean chili. See Table 2.1 for good dietary sources of iron. Remember that animal-based sources of iron are absorbed far better than plant-based sources. Although animal-based sources might not contain as much iron as those products that have been fortified with iron, the body will be able to use the iron more effectively if it comes from the animal-based source.

Calcium

Calcium intake is extremely important for athletes, especially females who might have less than adequate overall intake. The DRIs indicate that the recommended amount of calcium for girls ages 9–13 is 1,300 mg/day; for ages 19–50 it decreases to 1,000 mg/day and back up to 1,200 mg/day for women over 50 [7].

Table 2.1 Dietary sources of iron

	Serving size	Amount of iron (mg)
Animal based (better absorbed)		
Beef, chuck	3 oz	2.8
Pork	3 oz	1.3
Chicken, dark meat	3 oz	1.4
Plant based (not as easily absorbed)		
Soybeans	1/2 cup	15
Kidney beans, raw	1/2 cup	8
Black beans, raw	1/2 cup	8
Lentils, raw	1/2 cup	7
Post grape nuts (fortified)	1/2 cup	22
Quaker oatmeal squares (fortified)	1 cup	18
General Mill's total (fortified)	3/4 cup	18
Kellogg's all-bran complete (fortified)	3/4 cup	18

Based on data from USDA Nutrient Database for Standard Reference. Release 26, Software v.1.3.1 accessed 1/22/2014

There are 300 mg of calcium in one cup (8 oz) of milk which is one serving of dairy. Accordingly, the government recommends three servings of dairy or other calcium-rich foods per day. It is ideal to consume calcium in the diet; however, some women may need to take a calcium supplement to meet these DRIs. While it is important for athletes to get enough calcium, they do not have increased needs from those of non-athletes [4].

Recently Greek yogurt has become a popular dairy food, especially among athletes looking for the extra protein it provides. Women should be reminded, however, that Greek yogurt does not contain as much calcium as its non-Greek counterparts so if they are using it as a replacement for their dairy source, they should make sure to consume other additional sources. See Table 2.2 for select dietary sources of calcium.

Vitamin D

Vitamin D is important for the bones because it helps the body absorb calcium and higher intakes are linked with lower risk of stress fractures among youth [8]. It can be challenging to find dietary sources of vitamin D because it does not occur naturally in many forms except for some fish and mushrooms grown under special UV lights (see Table 2.3). However, many foods have vitamin D added to them. Any milk that is labeled as "fortified" is required to contain vitamin D. Other products such as enriched grains and cereals, yogurt, cheese, margarine, and juice have the option of adding vitamin D but are limited by the amount that they can

Table 2.2 Dietary sources of calcium

Food source	Serving size	Amount of calcium (mg)
Milk	8 oz	300
Cheese, provolone	1 oz	214
Cheese, mozzarella	1 oz	207
Cheese, cheddar	1 oz	204
Yogurt, non-Greek	6 oz	291
Yogurt, Greek	6 oz	187
Canned sardines with bone	3 oz	325
Soybeans, raw	3 oz	167
Tofu (with calcium sulfate)	3 oz	581
Soymilk (fortified)	8 oz	299
Rhubarb, cooked	1 cup	348
Almonds	1 oz	76
Orange juice (fortified)	8 oz	349
Broccoli	1 cup	43
Kale	1 cup	100

Based on data from USDA Nutrient Database for Standard Reference. Release 26, Software v.1.3.1 accessed 1/22/2014

Table 2.3 Dietary sources of vitamin D

Food source	Serving size	Amount of vitamin D
Fish oil (cod liver)	1 tbsp	1,360 IU
Mushrooms, portabella (with UV light)	1 cup	634 IU
Canned salmon	3 oz	493 IU
Milk (fortified)	8 oz	124 IU

Based on data from USDA Nutrient Database for Standard Reference. Release 26, Software v.1.3.1 accessed 1/22/2014

include and are not required by law to include it. If an athlete is worried about the amount of vitamin D that she is consuming or about a potential deficiency, it is best to read labels on specific foods rather than make assumptions. For example, one might think that because they get enough calcium from yogurt and cheese that they do not need to also drink milk. However, most cheeses and yogurts (especially Greek yogurt) are not fortified with vitamin D nor are they made from vitamin D-fortified milk [9]. Sunlight is the best source of vitamin D for the body so in the winter months (or if using sunscreen during the summer months), it is important to get enough from food sources or take a supplement if deemed medically necessary. For vitamin D the DRIs recommend women under the age of 70 consume 600 IU/day and over the age of 70, 800 IU/day [7]. See Table 2.3 for select dietary sources of vitamin D.

Supplements and Ergogenic Aids

Athletes should be counseled not to take any supplements or ergogenic aids without first checking with a medical provider, coach, or athletic trainer to ensure that it is a safe substance, that it is medically necessary for them to take, and that it is not a banned substance in their particular class of sport. For example, something as simple sounding as a vitamin enhanced with caffeine could have levels that are not allowed by the NCAA.

Sales of vitamins, supplements, and ergogenic aids are extremely high because these products make appealing promises to athletes: with one little pill you can improve performance, sleep better, have more focus, lose weight, etc. Like most promises such as these, they are too good to be true. Supplements are not regulated like food or medication are by the FDA, so sometimes ingredients are not all listed or the amounts of some ingredients might not be listed or may be inaccurate. Supplement companies are not required to verify the composition of their products before they go on sale to the public; only after they've been on the market and found to be unsafe are companies held accountable for this [4]. Athletes should be cautioned that taking a supplement could result in a positive urine test for a banned substance even if that ingredient is not listed. The best way for an athlete to avoid this unintended consequence is for that athlete to rely on real food and beverages rather than depending on a supplement to maximize performance. If athletes are taking supplements, it is important that they disclose all of them to their medical provider so that the potential for drug interactions can be reviewed.

While not recommended, not all supplements are bad and some, such as caffeine, have even been shown to improve performance in some studies [6]. Because many athletes take supplements regardless of whether or not there is scientific evidence to support their use, it is important not to approach the subject as a black or white issue. Explore why they are taking certain supplements and help them decide whether or not they are safe for continued use [4].

Hydration

For best performance, an athlete should begin exercising fully hydrated. That means being conscious of hydration status at all times, not just during a workout or when thirsty. Some people may complain that they do not like the taste of water, or cannot seem to remember to drink throughout the day. If possible, find ways to work around these barriers such as suggesting that they add lemon slices to water or eat fluid-packed snacks such as watermelon and cucumber. An athlete should consume 2–3 mL/lb of body weight of water 4 h before exercise in order to be fully hydrated and ready to perform [1]. For a 130-lb athlete that is a little over a cup of fluid. It was previously thought that caffeinated beverages would dehydrate rather than hydrate a person, but that has since been disproven [5]. However, an athlete should

consider whether or not caffeine is a banned substance in her organization before consuming caffeine prior to performance.

Even athletes who begin their workout hydrated can lose large amounts of water during exercise. The best way to find out just how much fluid a person is sweating out is to perform a sweat rate test. This can be done at home by taking weight pre-exercise and post-exercise using the equation below [5].

Sweat Rate Equation

$$\begin{aligned}&\left(\text{Pre-exercise weight in pounds} - \text{Post-exercise weight in pounds}\right)\\&\times 2.2\left(\text{kg}/\text{lb}\right)\times 1{,}000\left(\text{g}/\text{kg}\right) = \text{mL of fluid lost during exercise} / 29.5\left(\text{mL}/\text{oz}\right)\\&= \text{oz of fluid lost during span of exercise}\end{aligned}$$

This number might change depending on heat and the timing of exercise. As such, athletes should drink when thirsty and be mindful that urine is coming out light yellow to ensure adequate hydration status. Dehydration occurs when more than 2 % of body weight is lost without replacement and can cause detrimental effects such as muscle cramps [5].

During activity, electrolyte status must be considered in addition to hydration status. It can be helpful to consume a sport drink such as Gatorade that contains both carbohydrates and electrolytes when exercising for more than an hour. The sports drink should ideally contain 6–8 % carbohydrate [1].

After exercise is complete, it is important for an athlete to continue hydrating, both to make up for any fluids lost and not replaced during exercise and to remain properly hydrated for the next round of exercise. If dehydrated, rehydration post-exercise can be done by consuming 16–24 oz of fluid per pound of body weight lost during exercise, as determined by the sweat rate test [1].

Special Populations

Vegetarian and Vegan Athletes

Since many athletes are health conscious, they may be following a vegetarian or vegan diet due to the evidence that a primarily plant-based diet can prevent a host of chronic diseases. Or, they might avoid consuming animal products for ethical reasons. Whatever the origin, the vegetarian or vegan athlete needs to pay specific attention to several nutrients and ensure that adequate portions are consumed. First is protein; it is not sufficient to simply cut out meat without replacing it with a different source of protein. Good vegetarian protein sources include beans, lentils, tofu, eggs, nuts, seeds, and dairy. The next nutrient a vegetarian athlete should pay

special attention to is iron (see previous section for tips on consuming adequate iron). This is especially important because plant-based sources of iron (non-heme iron) are not absorbed by the body as well as animal sources (heme iron) are. Good vegetarian sources of iron include beans, lentils, leafy green vegetables, and enriched products such as cereal and bread.

Vegans who do not consume dairy need to make sure that they have an alternate source of calcium and vitamin D in their diet such as soy milk, cheese, or yogurt, tofu, leafy green vegetables, or fortified products such as orange juice or almond milk. Finally, a vegetarian athlete needs to be aware of her B12 consumption. Many vegetarian and vegan foods are fortified with B12, but if an athlete is not eating enough of these foods, she may require a B12 supplement.

Gluten-Free Athletes

About 1 % of Americans have celiac disease for which the treatment is to follow a diet free from gluten. A higher percent of people avoid gluten due to a sensitivity, a misconception that gluten or grain is "bad" for them, or a misconception that avoiding gluten can lead to weight loss. Whatever the reason for not eating gluten, an athlete can still eat a healthy, balanced diet that will provide enough carbohydrates for sustained energy. However, she will have to put effort into ensuring that she is getting enough carbohydrates in her diet and, for those with celiac disease, that the sources of carbohydrate have not been contaminated with gluten [6]. Carbohydrates are not only important in an athlete's diet for the purpose of providing sustained energy for exercise but also the preferred fuel of the brain. Needlessly cutting gluten from a person's diet can result in low carbohydrate intake, low iron or fiber intake (due to lack of iron-fortified grain products), and high cholesterol from increased animal product intake.

Foods that are high in carbohydrate but do not contain gluten include potatoes (white and sweet), corn, quinoa, rice (white, brown, wild), millet, amaranth, chickpeas, certified gluten-free oats, rice pasta, corn pasta, and gluten-free baked goods made from ingredients such as almond flour, rice flour, and potato flour.

Pregnant Athletes

Any athlete who is pregnant should consult a medical provider to make sure that the exercise plan that she has is safe and does not have the potential to cause harm to the mother or the fetus. The energy requirements listed previously in this chapter can be used for a pregnant athlete using the appropriate activity factor. For the first trimester this estimate of energy needs should suffice (i.e., no additional calories are necessary). For the second trimester an additional 340 cal/day is

suggested and for the third trimester an additional 452 cal/day [4]. Pregnant women should be counseled on eating recommended amounts of macro- and micronutrients, with a special emphasis on iron due to the increased blood supply, and folic acid due to the potential for birth defects associated with deficiency. Iron sources are listed in a previous section of this chapter. Sources of folic acid include dark green leafy vegetables, beans, lentils, and enriched grain products such as cereal, bread, pasta, and rice.

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Chapter 3
The Menstrual Cycle

Jennifer L. Carlson

Introduction

The menstrual cycle in females is vital for reproductive function, but can also be viewed as a sensitive marker, reflecting overall health status. The issue is so sensitive that many clinicians have advocated to have it included as a vital sign for all female visits [1]. Irregularity in the menstrual cycle is one of the components of the Female Athlete Triad, and may be the earliest marker of suboptimal health in this population. Interestingly, females with certain menstrual disorders and their associated findings may self-select into athletics as they have a natural advantage over normally menstruating peers (e.g., higher androgen levels in polycystic ovary syndrome (PCOS), longer bones/greater height in delayed puberty). However, menstrual disorders may also develop in the course of an athletic career and place athletes at risk for ensuing complications.

The Normal Menstrual Cycle

Before defining abnormalities, it is important to establish the normal pattern of menses. Age of menarche varies between countries and has been declining over the past century. Within the United States, the median age of menarche is 12.43 years

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with 80 % of girls reaching menarche between the ages of 11.0 and 13.75 years [2]. Approximately 98 % of girls have begun menstruating by the age of 15 years [1]. Once menarche has occurred, cycles may take up to 2 years to become regular, ovulatory cycles; they may be "regularly irregular." Although cycles may not be occurring monthly, they tend to vary between 21 and 45 days [1]. Within the first year, approximately 50 % of cycles may be anovulatory though 80 % will fall within the 21–45 day range. By 3 years post-menarche, 95 % of menstrual cycles fall within this time range [3].

Menstruation is controlled by the hypothalamic-pituitary-ovarian (HPO) axis. Gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile fashion by the hypothalamus and stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH, in turn, act on the ovary to stimulate development of a primary follicle and production of estradiol which acts in a positive-feedback loop on the hypothalamus. Once a critical level of estradiol is reached, a GnRH pulse triggers a surge in LH levels and ovulation occurs. Upon ovulation, a corpus luteum is formed which produces progesterone to support the endometrium in anticipation of a fertilized egg. If no implantation occurs after approximately 14 days, the corpus luteum regresses and progesterone levels drop. Because the endometrium is no longer supported by progesterone, the uterine lining is sloughed and menstruation occurs.

Definitions of Common Menstrual Disorders in Athletes

Menstrual disorders in athletes widely range from luteal phase defects to oligomenorrhea, primary- and secondary amenorrhea.

Luteal phase defects are subclinical menstrual disorders that result from decreased estrogen levels in the early follicular phases and a decreased LH pulse frequency. Follicular development is reduced, ovulation is delayed, and the corpus luteum's secretion of progesterone is diminished. Luteal suppression can be defined by a luteal phase less than 11 days or a setting of low progesterone [4, 5]. Clinically, this results in regular menses, but a young woman will be infertile due to the lack of progesterone to support the endometrium.

Oligomenorrhea is defined as menses occurring at intervals greater than 45 days (with concern raised when the interval is greater than 35 days after the first post-menarchal year), but typically less than 3 months apart, or with four to nine menses in the past year.

Primary amenorrhea is the lack of spontaneous menses in a female with normal secondary sexual development. In the past, 16 years of age was the time to initiate a work-up in a female with primary amenorrhea. Current recommendations have changed and if an adolescent has not reached menarche by 15 years, she is considered to have primary amenorrhea and a work-up is warranted [6].

Secondary amenorrhea reflects amenorrhea in a woman who has already established menstrual periods. Generally, the term secondary amenorrhea is used once 3 months have passed without a menses.

Epidemiology of Menstrual Disorders in Athletes

Menstrual disorders in female athletes occur frequently. In a recent meta-analysis of studies describing prevalence of the different Triad components, a large range in the frequency of menstrual disorders was noted. Primary amenorrhea ranged from 0 to 56.0 %, oligomenorrhea from 0.9 to 52.5 %, and the subclinical menstrual disorders of luteal phase defects and anovulation from 5.9 to 43.0 % and 12.0 to 30.0 %, respectively [7]. In a study by De Souza, exercising women were found to have a 79 % incidence of luteal phase defects over a 3-month span [8]. These large ranges may reflect the different types of athletes sampled or the methods used to collect data; however, they indicate that menstrual dysfunction is not an uncommon phenomenon in athletes. By comparison, menstrual dysfunction in the form of secondary amenorrhea in the general population is estimated at 2–5 % [9–11]. Aesthetic, endurance, and weight class-based sports, in addition to higher training volumes and lower body weights seem to place athletes at greater risk for menstrual disorders [12–14].

Based on the physiology of the menstrual cycle, one would expect to see more menstrual dysfunction in younger athletes. Although irregularities are increased in younger women, research has shown that irregularities are present in women of all different ages. In a study comparing high school athletes to sedentary students, 54 % of athletes reported abnormalities (primary, secondary, or oligomenorrhea) versus 21 % of the sedentary students [15]. Another study of high school athletes described a rate of 23.5 % for menstrual irregularity [16]. A study of college-aged women reported a 26 % frequency of menstrual dysfunction [17]. In a study of runners aged 18–25 years, 36 % of the athletes had abnormal menses: 10 % with amenorrhea, 26 % with oligomenorrhea [18].

Several studies have noted a later age of menarche for athletes, although the underlying etiology remains unclear (self-selection versus exercise-related) [19]. Frisch et al. noted that among a group of college athletes, each year of training before menarche delayed menarche by 5 months [20]. Research has suggested that the intensity of exercise may affect timing of menarche [21]. In a study of women at different exercise levels, athletes had later menarche than non-athletes, and Olympic-level athletes had later menarche than high-school-level or collegiate-level athletes [22]. The type of sport may also play a role in timing of menarche [19, 23]. Among Norwegian elite athletes and controls, menarche occurred later in the athlete group [23]. Additionally, athletes participating in leanness sports, defined as sports that place a competitive or aesthetic value on a lean physique such as distance running, were significantly more likely to have menstrual dysfunction (24.8 %) than athletes in non-leanness sports (13.1 %) and controls [23].

Etiology of Menstrual Dysfunction

Disruption of the HPO axis is thought to be the most common cause of menstrual dysfunction in the female athlete. This disruption is attributed to a decrease in GnRH pulsatility that causes reduced secretion of LH and FSH by the pituitary.

The reduced levels of LH and FSH result in less stimulation to the ovary and decreased amounts of estrogen production. Depending on the degree of HPO suppression, the effects on the menstrual cycle can vary from subclinical (luteal phase defects) to completely shut down (amenorrhea). (Please see Chap. 6: Neuroendocrine Abnormalities in Female Athletes.)

Knowledge regarding the mechanism for HPO axis suppression, or hypothalamic amenorrhea, has evolved over recent years [24]. It was once thought that the stress associated with the physiological demands of intense exercise was the cause of disruption. Some recent studies have refuted that idea [23, 25]. Another previous theory was the body fat threshold requirement that suggested a certain level of body fat, which may be lacking in some athletes, is needed to maintain regular menstruation. A meta-analysis done by Redman and Loucks reviewed 28 studies comparing amenorrheic and eumenorrheic athletes and found that there was a 2.2 % lower body fat content in amenorrheic athletes [13]. However, given the 14 % range of sample means in both groups, they concluded a difference of 2.2 % was likely not a significant contributor to the underlying etiology of menstrual dysfunction.

Current thought is that hypothalamic amenorrhea in athletes is secondary to an insufficient energy state or "energy deficit" [24]. In a study by Loucks, LH pulsatility was disrupted within 5 days when energy availability fell below 30 kcal/kg/day, as compared to the estimated needs of 45 kcal/kg/day for a healthy woman [26]. Leptin has become a hormone of increasing interest as the link between energy balance and menstrual function. Leptin, a hormone secreted by adipose cells, regulates food intake and energy balance and has levels that correspond to fat mass and acute nutritional changes. Low leptin and high ghrelin levels have been associated with lower LH secretion in amenorrheic athletes compared to eumenorrheic female athletes [27]. It is thought that a starvation state, even if short term, causes a decrease in leptin levels as an adaptive survival mechanism to reduce energy expenditure associated with reproductive function [28]. In a study of leptin administration to women diagnosed with hypothalamic amenorrhea, six of the eight women exhibited improvement or normalization of LH pulsatility after receiving leptin compared to the control group [29].

In addition to leptin, the mechanism of GnRH suppression is moderated by several different factors including ACTH and cortisol, and reflects a variety of different factors such as amount and intensity of athletic training, type of training, and timing of training initiation [30]. For example, cortisol levels, known to be increased in eating disorders, were inversely associated with LH pulsatility [31].

Although hypothalamic dysfunction is a primary mechanism mediating menstrual disorders in female athletes, it should be considered a diagnosis of exclusion and a thorough work-up is warranted to evaluate other potential etiologies. Hyperandrogenism, as associated with PCOS, is the most common hormonal abnormality affecting menstrual function in women. Athletes are not immune and some studies suggest that individuals with hyperandrogenism may self-select for athletics as the increased androgens may confer athletic advantages. Some research has suggested that hyperandrogenism may explain reproductive dysfunction in some elite

athletes at rates higher than previously expected [32–34]. In a study of 90 Swedish Olympic athletes, the majority of menstrual disturbances were attributed to PCOS rather than hypothalamic suppression [33]. In a different study of swimmers, delayed puberty and menstrual irregularities were common, but hormone profiles were more consistent with mild hyperandrogenism than with hypothalamic amenorrhea [32].

Evaluation of Menstrual Abnormalities

To evaluate primary or secondary amenorrhea in an athlete, it is important to perform a thorough history and physical examination. Within the medical history, one should assess concurrent medical issues, medication use, timing of pubertal development (breast development, pubic hair development), and age of mother's and any sister's menarche. Additionally, questions about eating history, concerns about weight and shape, and exercise history are essential. Energy imbalance cannot be ascertained by a patient's appearance or weight alone; rather, a detailed dietary and activity recall will help determine if the caloric intake is sufficient to cover the level of exercise and physiologic function for that individual. A dietician's input in this evaluation can be critical, as the caloric demands of different activity levels and different ages can vary greatly.

Some basic laboratory tests can be used to help elucidate the cause of the menstrual dysfunction. The American Society of Reproductive Medicine suggests an initial screen with a pregnancy test, FSH, thyroid-stimulating hormone (TSH), and prolactin levels [6]. Additionally, measuring LH, estradiol, androgen levels, and an early morning 17-hydroxyprogesterone can further narrow one's diagnosis [35] (Table 3.1).

Table 3.1 Serum evaluation for amenorrhea

Test	Finding
Beta human chorionic gonadotropin	Pregnancy
FSH	↓ in HPO suppression
	↑ in primary ovarian insufficiency
LH:FSH	May see >2:1 in PCOS
Estradiol	↓ in HPO suppression
TSH	Thyroid dysfunction
Prolactin	↑ in pituitary tumor
Androgens	
Free testosterone	↑ in PCOS
Dehydroepiandrosterone sulfate (DHEA-S)	↑ in adrenal hyperplasia/tumor
17-Hydroxyprogesterone[a]	↑ in adrenal hyperplasia

[a]To be drawn as an early morning sample

Primary Amenorrhea

It is important to remember that any cause of secondary amenorrhea can be a cause of primary amenorrhea (see Table 3.2). Additionally, one should focus on possible anatomic or chromosomal abnormalities as the cause of primary amenorrhea. Anatomic abnormalities can include imperforate hymen, vaginal agenesis/Mullerian agenesis, or transverse vaginal septum. While some of these findings may be visualized on an external pelvic exam, one may also need to perform a pelvic ultrasound in order to ascertain the pelvic anatomy. Pubertal timing can be key to identifying underlying chromosomal abnormalities. In normally developing adolescents, menarche follows breast development, thelarche, within 2–3 years. If breast development has not begun or if it has occurred greater than 3 years

Table 3.2 Etiologies of primary and secondary amenorrhea

Hypothalamic	Immaturity of the HPO axis
	Eating disorders
	Exercise-induced amenorrhea/ Female Athlete Triad
	Medication-induced amenorrhea
	Chronic illness
	Stress-induced amenorrhea
	Kallman syndrome
Pituitary	Hyperprolactinemia
	Prolactinoma
	Craniopharyngioma
	Isolated gonadotropin deficiency
Thyroid	Hypothyroidism
	Hyperthyroidism
Adrenal	**Congenital adrenal hyperplasia**
	Cushing syndrome
Ovarian	Polycystic ovary syndrome
	Gonadal dysgenesis (Turner Syndrome)
	Primary ovarian insufficiency
	Ovarian tumor
	Chemotherapy, irradiation
Uterine	Pregnancy
	Androgen insensitivity
	Uterine adhesions (Asherman syndrome)
	Mullerian agenesis
	Cervical agenesis
Vaginal	**Imperforate hymen**
	Transverse vaginal septum
	Vaginal agenesis

Adapted from Golden NG, Carlson JL. The pathophysiology of amenorrhea in the adolescent. Ann NY Acad Sci 2008; 1135:163-178. With permission from John Wiley & Sons, Inc. *Bolded* disorders indicate causes of primary amenorrhea only

ago, one should consider an underlying chromosomal issue. Chromosomal abnormalities, indicated by an abnormal karyotype, include androgen insensitivity and Turner syndrome.

Secondary Amenorrhea

In secondary amenorrhea, one is not as concerned about primary anatomic abnormalities since the outflow tract is assumed to be patent given menses have previously occurred. Rather, clinicians should focus on hormonal abnormalities that could be affecting normal menstrual function. These hormonal abnormalities are generally thought to be due to hypothalamic suppression, hyperandrogenism such as PCOS, elevated prolactin levels, or thyroid dysfunction. While several of these etiologies can be suggested by history and physical examination, laboratory evidence is usually required to make the diagnosis. Of clinical note, thyroid levels can be affected by hypothalamic suppression and may not reflect an underlying thyroid disorder. In hypothalamic suppression, one will typically see a low to normal TSH and low triiodothyronine (T3) levels [36].

Treatment of Menstrual Disorders

Treatment of the menstrual dysfunction depends on the underlying issue identified. In athletes with hypothalamic amenorrhea, restoring a normal energy balance is critical to normal hormonal resumption and, ultimately, normal bone accrual and development. As recommended in the International Olympic Committee position stand on the Female Athlete Triad, increasing dietary intake is the first step [37]. If an athlete is unwilling or unable to make appropriate dietary changes, then reducing exercise is another option. Once a more favorable energy balance is obtained, it can still take several months to a year for normal menses to resume [38]. During this time, clinicians can be monitoring serum levels of LH, FSH, and estradiol every 3 months to follow any trends. Low levels of LH, FSH, and estradiol indicate continued hypothalamic suppression. In a study of patients with eating disorders, Golden found that an estradiol level above 30 pg/mL is associated with menstrual resumption within 3–6 months in 90 % of patients [39].

Hormone Therapy in Primary Amenorrhea

In athletes with primary amenorrhea, one may consider the use of hormone replacement therapy (HRT) for the treatment of hypothalamic amenorrhea, as seen with anorexia nervosa, exercise-induced amenorrhea, and premature ovarian insufficiency [40]. The primary goals of HRT are to induce age-appropriate secondary

sexual characteristics and to maximize skeletal health, although there is still limited research on the appropriate dosing for optimizing these outcomes [41]. Composed of three main phases, HRT should be individualized for each patient based on her physical and psychological needs and readiness [40]. In Phase 1, lower-dose estrogen monotherapy is used, either in a transdermal or oral preparation, to mimic the early phases of puberty in which estrogen is unopposed. During this phase, breast development and growth are stimulated. In Phase 2 of treatment, the estrogen dosages are increased, as would correspond to the hormonal shifts in a typical pubertal progression. Additionally, progestin therapy is begun to induce and maintain regular menses. Once menses have been established, Phase 3, or maintenance phase, commences in which adult serum levels of estrogen are achieved and maintained. A variety of hormonal preparations may achieve this, including combined estrogen/progesterone products in oral, transdermal, or transvaginal delivery modalities.

Hormone Therapy in Secondary Amenorrhea

The use of oral contraceptive pills to resume menses in athletes with secondary amenorrhea is often recommended by some providers, but has little evidence to support its prescription [30, 42–46]. While using oral contraceptive pills may restore regular bleeding episodes, it does not restore the energy and hormonal balance that is critical for maximum bone development. Additionally, since regular periods are an important marker of a healthy weight and body, masking menstrual resumption with pill-induced menses results in a loss of an important clinical tool.

Conclusion

Menstrual irregularity is a common, but not a normal, finding in female athletes that encompasses a range of disorders. A thorough evaluation is warranted to investigate potential etiologies. Recent research is helping to define the underlying mechanisms of menstrual dysfunction with the leading theory being one of an insufficient energy state disrupting the HPO axis. If the Female Athlete Triad is suspected with HPO axis suppression, then restoring an appropriate energy balance is key to restoring menstrual function and maximizing health.

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Chapter 4
Exercise and the Female Skeleton

Leigh Gabel and Heather M. Macdonald

Introduction

The ability of bone to adapt to loads associated with physical activity was first described more than a century ago [1, 2]. In recent decades, a substantial body of evidence has evolved to support an integral role for physical activity and weight-bearing exercise[1] in the development and maintenance of a healthy skeleton. In particular, the critical period of childhood and adolescence, when more than one-quarter of adult bone mass is accrued [4], represents a window during which the skeletal benefits of weight-bearing activity can be optimized [5–12]. In turn, physical activity during growth is thought to be one of the most effective strategies to prevent osteoporosis and related fractures later in life.

Although we do not yet know the precise exercise prescription for optimal bone health, evidence from animal studies and several school-based intervention studies suggests that "a little goes a long way." Specifically, short bouts of high-impact physical activity implemented over relatively short timeframes may be sufficient to enhance bone mass accrual during growth. Conversely, we know less about the

[1] Physical activity is defined as any body movement that increases energy expenditure, while exercise refers to planned physical activities that enhance or maintain physical fitness [3].

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influence of weight-bearing activity on bone *structural* adaptations to weight-bearing exercise that in turn influence bone strength during growth and into young adulthood. Bone strength is undeniably the most important parameter for describing skeletal health [13, 14], and it is this tenet that has guided a paradigm shift away from assessing only 2D measures of bone mass (measured with dual energy X-ray absorptiometry, DXA) to 3D measures of bone structure and microarchitecture. As the use of imaging devices such as peripheral quantitative computed tomography (pQCT), high-resolution pQCT, and magnetic resonance imaging (MRI) increases, we are beginning to understand more completely the hierarchical structure of bone, and how this complex structure adapts to exercise. In addition, these tools permit more accurate assessment of skeletal health in female athletes who demonstrate low energy availability and menstrual dysfunction.

In this chapter, we begin with a brief overview of the mechanisms by which bone adapts to exercise and the imaging tools commonly used to measure these changes in the growing and mature skeleton. We then discuss the influence of exercise on bone strength in childhood, adolescence, and early adulthood, with a specific focus on studies in girls, including female athlete triad populations. We acknowledge that DXA studies have considerably advanced our understanding of bone adaptations to physical activity, and we direct the reader to several excellent reviews of DXA-based studies [5, 9, 15]. However, in this chapter we focus, whenever possible, on studies that employed 3D imaging tools.

How Bone Adapts to Exercise

In this section, we review the mechanisms by which bone adapts to mechanical stimuli, whether through exercise or activities of daily living. Bone is a complex and dynamic tissue whose primary role is to provide structural support and withstand loads imposed by both external and internal forces (e.g., gravitational and muscular forces) [16]. The skeleton is continually exposed to a loading environment, and bone is deposited and resorbed in such a fashion as to achieve an optimum balance between bone strength and weight [17].

As early as the nineteenth century, Julius Wolff and others described how the architecture of bone adapts to the mechanical loads applied to it, remodeling over time to better resist similar strains [2]. Bone responds to mechanical loading through mechanotransduction, a process through which a biophysical force is converted into a cellular response [18]. Although the exact cellular mechanisms are still poorly understood, mechanical strain in bone tissue is sensed by osteocytes and a signaling cascade is initiated to the effector cells (osteoblasts and osteoclasts) [18]. The skeleton responds to the imposed mechanical strains through bone modeling (during growth) and remodeling and adjusts bone mass and structure accordingly to match the requirements of the mechanical environment [17, 19]. Frost's mechanostat theory and the functional model of bone development propose that the growing

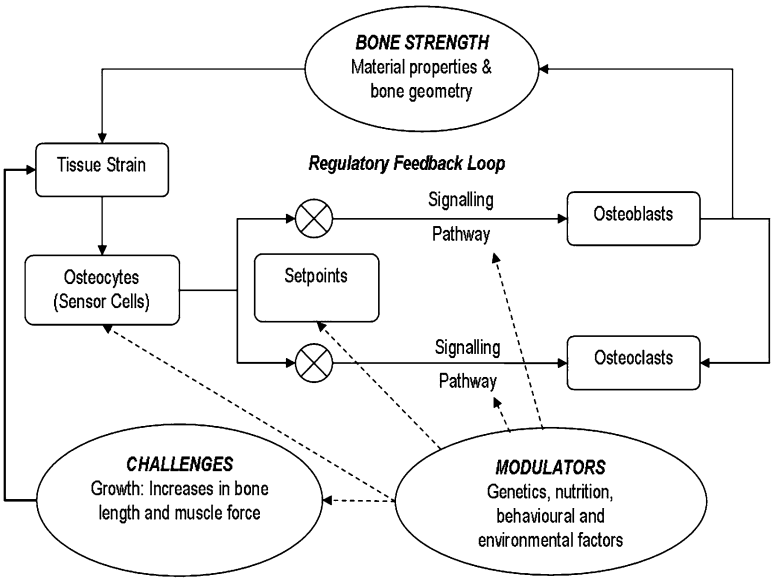


Fig. 4.1 The functional model of bone development based on the mechanostat theory [20] and related approaches [19]. The feedback loop between bone deformation (tissue strain) and bone strength is central to regulation of bone adaptation. Various modulating factors influence aspects of the regulatory system as indicated by the *dashed arrows*. [Adapted from Rauch F, Schoenau E. The developing bone: slave or master of its cells and molecules? Pediatr Res. 2001 Sep;50(3): 309–14. With permission from Nature Publishing Group]

skeleton endeavors to keep bone tissue strain at an optimal level, and that a negative feedback loop between tissue strain and bone strength is central to bone's regulation (Fig. 4.1) [19, 20]. The negative feedback loops are influenced by mechanical and nonmechanical factors [19, 20]. The primary mechanical challenges to the skeleton during growth are increases in body weight and muscular forces. These heightened loads during growth increase bone tissue strain above a set point necessary to induce bone modeling. Following skeletal maturity, peak bone tissue strains are reduced and result in conservatory remodeling. While mechanical stimulation is the key to structural integrity, the mechanostat set points may be altered by nonmechanical stimuli such as hormones and nutrition [19].

Our understanding of bone adaptation to loading has been greatly enhanced by experimental evidence from animal models [21–27]. Based on this evidence, Charles Turner proposed three fundamental "rules" that predict bone structural adaptations to mechanical stimuli [28]. First, dynamic loading drives bone adaptation (as opposed to static loading). Further, the stimulus for bone adaptation increases with the magnitude or frequency of the loading. Second, only short bouts of mechanical loading are necessary to elicit an osteogenic response. There is a ceiling effect

for bone tissue stimulation, whereby bone adaptations are subject to diminishing returns beyond a certain loading frequency or duration. Third, bone cells become accustomed to routine strain and structural change is driven by abnormal strains. These "rules" provide insight into how different intensities and modalities of exercise predict bone adaptation in humans.

During growth, bone can adapt its strength in response to mechanical stimuli through several different mechanisms: (1) periosteal apposition can increase bone cross-sectional area (CSA); (2) periosteal apposition in conjunction with reduced endocortical resorption can increase cortical thickness; and/or (3) modifications to cortical and trabecular microarchitecture (i.e., increased trabecular thickness or number or decreased cortical porosity) can increase tissue density [7, 29]. In contrast, the mature skeleton appears to preferentially adapt to loading through gains in bone density as evidenced by results from animal studies [30]. Further, animal studies also demonstrate a greater capacity of the growing skeleton to adapt to mechanical loading than the mature skeleton [31, 32].

Muscle–Bone Relationship

Frost's mechanostat theory and the functional model of bone development contend that bone continually adapts to increased mechanical loads through changes in mass, structure, microarchitecture, and strength in order to maintain strains within safe limits [19, 20]. Muscle contractions pose the greatest mechanical challenge to bone (stresses several-fold greater than body weight alone) and are the primary driving force of bone adaptation. If, as suggested by the functional model of bone development, increasing muscle forces provide the stimulus for increases in bone mass, structure, microarchitecture, and strength, it stands to reason that muscle development should precede bone development. Longitudinal data from the University of Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS) provide evidence for this phenomenon. First, Rauch et al. demonstrated that velocities of total lean body mass (LBM; surrogate of muscle force) precede peak BMC accrual (by DXA) by approximately 6 months in girls and 4 months in boys [33]. Additionally, peak LBM preceded peak BMC in 87 % of girls and 77 % of boys [33]. In a subsequent analysis using hip structural analysis (HSA), velocities of total LBM accrual peaked prior to velocities of bone CSA and estimated bone strength (section modulus) at the narrow neck and femoral shaft by 2–4 months (Fig. 4.2) [34]. These findings support the theory that increases in muscle mass peak prior to increases in bone mass and suggest that the stimulus of muscle drives bone growth. However, the relationship between bone and muscle might not be uniform throughout the skeleton and may be site specific. For example, Xu et al. noted that muscle CSA (surrogate of muscle force) at the tibial shaft (by pQCT) peaked prior to BMC and BMD, but lagged behind that of total and cortical bone CSA [35]. We discuss several studies that imply muscle forces mediate the exercise–bone relationship [36, 37] in greater detail below.

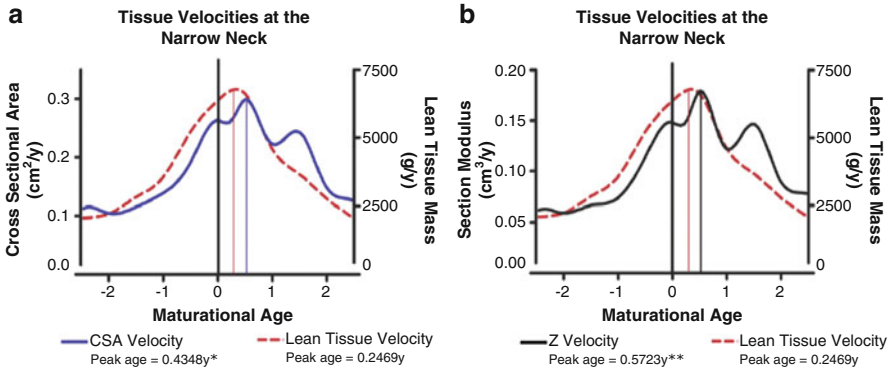
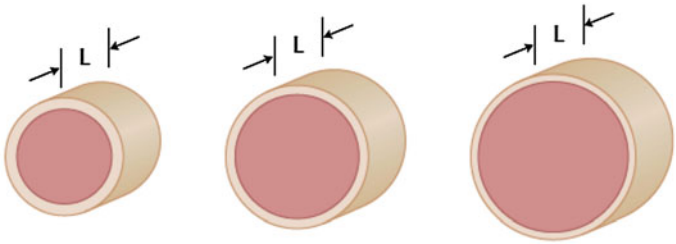


Fig. 4.2 Tissue velocity curves for lean tissue mass, (**a**) cross-sectional area (CSA) and (**b**) section modulus at the narrow neck region of the proximal femur aligned by maturation in girls and boys. The maturational age of 0 represents the age at peak height velocity (12.49 years). The *solid drop down lines* landmark the maturation age at which the peak tissue velocities occur. *Single asterisk* indicates a significant difference between the age of peak lean tissue velocity (PLTV) and peak CSA velocity. *Double asterisk* indicates a significant difference between PLTV and peak section modulus velocity. [Reprinted from Jackowski SA, Faulkner RA, Farthing JP, Kontulainen SA, Beck TJ, Baxter-Jones ADG. Peak lean tissue mass accrual precedes changes in bone strength indices at the proximal femur during the pubertal growth spurt. Bone. 2009 Jun;44(6):1186–90. With permission from Elsevier]

How to Measure Bone Adaptation to Exercise

In this section, we briefly discuss commonly used densitometric techniques, but refer the reader to Chap. 5 for more detail regarding the assessment of bone health in the young athlete. DXA is often the imaging device of choice in clinical bone health research due to its relative ease of use, low radiation dose, and ease of assessment of BMC and aBMD at clinically relevant sites such as the lumbar spine and hip. However, DXA's planar nature is unable to account for bone depth and this limitation precludes it from assessing the distribution of bone mass [38]. As a result, DXA-based measures of bone mass and aBMD are highly influenced by bone size, systematically underestimating aBMD in short individuals and overestimating aBMD in taller individuals [39]. This issue is particularly problematic when assessing bone in the growing skeleton, whether making comparisons between individuals of different sizes or within the same individuals longitudinally. Several strategies have been proposed to account for DXA's size dependency by adjusting for body size and composition variables such as height, bone area, maturity, and mass [40]; however, even with such adjustments, DXA is still limited by its inability to assess 3D cross-sectional geometry and differentiate between cortical and trabecular compartments.

Bone's complexity and mechanical competence cannot be adequately described by simply the amount of bone present. As mentioned previously, measures of BMC and



Outer diameter, *cm*	2.5	3.0	3.5
BMD	1.0	1.0	1.0
vBMD	1.20	1.0	0.86
BMC or bCSA	0.83	1.0	1.17
CSMI	0.58	1.0	1.55
Section modulus	0.70	1.0	1.33

Fig. 4.3 Scale drawing of three-cylindrical cross sections with different outer diameters, but fixed region length (*L*) and equivalent areal bone mineral density (BMD). The outer diameter, volumetric BMD (vBMD), bone mineral content (BMC), cross-sectional moment of inertia (CSMI), and section modulus are also shown. BMC is not equivalent to CSA excluding spaces occupied by soft tissue (bCSA), but in a cross section they scale linearly. [Reprinted from Beck TJ. Extending DXA beyond bone mineral density: understanding hip structure analysis. Curr Osteoporos Rep. 2007;5:49–55. With permission from Springer Verlag]

aBMD do not reflect where bone is located. As bone bending strength varies exponentially with the distance from the center of mass of the cross section, less material is needed for the same bending strength as the diameter increases. Thus, when investigating bone adaptation to exercise, important properties of whole bone strength such as structure and microarchitecture must be considered. This is highlighted by several animal studies that demonstrated how minimal exercise-induced increases in DXA-derived BMC and aBMD (<10 %) are accompanied by substantial increases (>60 %) in bone strength measured by micro-CT [41, 42]. Further illustrating this phenomenon is a schematic representation that demonstrates marked variation in bone bending strength (section modulus) despite identical aBMD (Fig. 4.3) [43].

HSA is often applied to 2D DXA images to estimate bone cross-sectional geometry and bone strength at three locations of the proximal femur [44]. HSA has figured prominently in the bone literature in the last decade; however, this tool suffers from the same limitations as DXA [45]. Thus, we must consider 3D imaging techniques such as pQCT, HR-pQCT, and MRI to more accurately measure bone structure and microarchitecture, and estimate bone strength.

Unlike DXA, QCT imaging modalities directly measure bone cross-sectional geometry and volumetric BMD (g/cm^3) for a given region of interest. pQCT and HR-pQCT are used to assess the appendicular skeleton and are relatively common in pediatric research due to their short scan time and minimal effective radiation exposure. pQCT is typically used to assess bone structure at distal and shaft sites of the tibia and radius. Bone strength in compression can be estimated at distal sites using bone strength index (BSI, mg/mm^4; incorporates CSA and BMD) and in bending or torsion at shaft sites using polar strength–strain index (SSI_p, mm^3; density-weighted

section modulus). Additionally, reference data are available for children and young adults for cortical and trabecular BMD, CSA, and cortical thickness [46, 47]. In contrast to pQCT measures at the radius, tibial pQCT measures provide structural information at a weight-bearing site. Despite these advantages, pQCT is limited by a maximum imaging resolution of 0.2 mm and is, therefore, unable to accurately assess trabecular bone microarchitecture, or separate cortical and trabecular bone in regions where the cortex is quite thin, such as the distal radius [48]. HR-pQCT, on the other hand, has an imaging resolution of 82 μm. This resolution permits accurate assessment of trabecular microarchitecture, such as trabecular number and thickness [49]. Cortical porosity can also be quantified using customized software [50, 51] and compressive bone strength can be estimated using finite element analysis [52]. Although limited to assessments of the peripheral skeleton, strong correlations are observed in adults between bone stiffness measures at distal sites by HR-pQCT and finite element analysis and at the lumbar spine and proximal femur using central QCT [53]. Thus, the mechanical competence of sites such as the distal radius and distal tibia are likely reflective of central, clinically relevant sites. Nevertheless, making comparisons between studies can be challenging since pQCT and HR-pQCT acquisition and analysis protocols are not yet standardized.

MRI is a unique bone-imaging tool as it does not emit ionizing radiation and can acquire multiplanar images without repositioning [54]. MRI is also able to assess trabecular and cortical bone using recent image acquisition and processing techniques [55]. Unlike pQCT, MRI is able to scan whole bones and several limbs simultaneously. However, MRI technology is expensive and scan times are considerably longer than DXA and pQCT, ranging from 10 to 30 min depending on the imaging sequence used [56]. Further, quantification of trabecular microarchitecture measures such as thickness and number are challenging and techniques are still being developed. Thus, until recently, the pediatric MRI literature has focused on bone structure as opposed to bone microarchitecture [57, 58].

Advances in bone imaging technologies now permit us to evaluate the subtle adaptations in bone structure and microarchitecture that underpin changes in bone strength across the lifespan. In addition, these technologies are expanding our understanding of how the skeleton adapts to exercise beyond what is already known from traditional DXA-based techniques.

How Exercise Influences Bone Development in Children and Adolescents

We have known for more than two decades that lifestyle habits adopted during childhood and adolescence have the potential to prevent osteoporosis [59]. The positive influence of exercise on bone development is summarized in several excellent reviews [5–12]. Specifically, there is strong evidence to suggest that pre- and early puberty may provide a “window of opportunity” during which the skeleton is particularly responsive to loads associated with weight-bearing activity [9, 15]. In contrast, we know less about the mechanisms underpinning bone’s adaptation to

exercise in later adolescence [5, 60–63]. This may be due, in part, to the reliance on DXA in previous studies of this age group, which may have prevented subtle, but important adaptations in bone structure from being captured.

Before discussing details of important studies in this area, we briefly review the normal pattern of bone accrual in childhood and adolescence. Several longitudinal studies have advanced our understanding regarding the timing and magnitude of bone mineral accrual during the growing years [35, 64–66]. One of the most widely cited studies, the University of Saskatchewan PBMAS, followed approximately 200 healthy children for 7 years and conducted annual bone mass measures by DXA [64]. The authors controlled for maturational differences by aligning children on a common maturational landmark, peak height velocity (PHV), and found that total body bone mineral accrual occurred about 1.4 years earlier in girls, and was of a smaller magnitude than in boys. Approximately 35 % of total body and lumbar spine BMC and greater than 27 % of femoral neck BMC was accrued during the 2 years around PHV [4]. Further, 33–46 % of adult BMC was accrued across the entire 5-year period of adolescent growth [65]. This represents double the bone mass that will eventually be lost between the age of 50 and 80 years in women [67]. This period is also critical for development of bone structural properties that contribute to bone strength [35, 66] Thus, it is during childhood and adolescence that the foundation for adult bone health is established. While our skeletal blueprint is largely determined by genetics [68–70], we know that exercise and physical activity play a key role in optimizing bone accrual during growth.

Intervention Studies

Targeted bone-loading programs have traditionally been implemented in elementary schools due to the ease with which large numbers of children from diverse backgrounds can be reached. Effective programs incorporated dynamic, high-impact activities that were of short duration, elicited “unusual” strains and were separated by rest periods, thus mirroring the principles derived from the animal literature [71]. These studies ranged in duration from 3 to 48 months, and most used DXA to monitor exercise-related gains in bone mass [5, 12]. Importantly, children assigned to exercise intervention groups gained significantly more bone mass (1–6 %) at the spine and hip compared with children in control groups [5].

In the longest school-based randomized controlled trial conducted to date, the University of British Columbia’s Healthy Bones Study (HBS), children (aged 9–11 years) attending schools randomized to the exercise group participated in 10–12 min of high-impact jumping activities, three times/week [72, 73]. After the first school year, girls and boys attending intervention schools demonstrated significantly greater gains in bone mass at the femoral neck and lumbar spine compared with children attending control schools; however, in girls the intervention effect was only apparent in those who were early pubertal (Tanner stage 2 or 3) at baseline [74, 75]. After 2 school years, significant gains in femoral neck (5 %) and lumbar spine (4 %) BMC were observed in girls [72] and gains in femoral neck (4 %) BMC were observed in boys [73].

The HBS, and others like it, highlights that a simple exercise program, which requires very little time in the school day, may enhance children's bone health.

Animal models clearly demonstrate that the skeleton adapts to mechanical loading by adding bone to the periosteal surface of long bone shaft sites where strains are the greatest [71, 76]. Although small in magnitude, these subtle structural adaptations confer dramatic increases in experimentally measured bone strength [41, 42]. As mentioned previously, DXA is unable to capture such adaptations to exercise. Only 11 (8 involved only girls) of the intervention trials conducted in the last decade used imaging tools such as HSA, pQCT, or MRI to assess exercise-induced changes in bone structure and strength [12]. In the HBS trial, the greater gain in femoral neck BMC in early pubertal girls in the intervention group was associated with a 4 % greater increase in femoral neck bone strength (section modulus, HSA) compared with controls after 7 months [29]. This strength gain was attributed to reduced endosteal resorption, leading to a greater increase in CSA and a thicker cortex in the intervention group. In contrast, intervention-related gains in femoral neck bone strength were only observed in boys after the second year of the trial [73]. The apparent sex difference in the timing of structural adaptations to the HBS intervention is likely related to maturity status. At baseline, 60 % of girls were early pubertal, whereas the majority of boys were prepubertal. The later adaptation in bone strength in boys may be a result of advanced maturity (77 % advanced to early- or peri-puberty) over the second year of the study and/or the prolonged intervention. These findings suggest that early puberty may be a window of opportunity for femoral neck bone strength adaptations. A more intense exercise intervention may also be necessary to confer structural adaptations at the hip during prepuberty.

The influence of maturity status on bone structural adaptations to exercise may also vary with skeletal site. In the Action Schools! BC (AS!BC) trial, which involved short bouts of classroom-based exercise (including ~3 min/day of jumping), girls in intervention schools that reported high compliance (≥80 %) demonstrated 5 % greater gains in femoral neck bone strength (section modulus, HSA) compared with girls in control schools [77]. Conversely, an intervention effect was not observed at either the distal or shaft site of the tibia (by pQCT) in girls [78], the majority of whom were early pubertal at baseline. As prepubertal boys in the intervention group demonstrated a 4 % greater gain in distal tibia bone strength (BSI) compared with controls, it is possible that the appendicular skeleton is more responsive to loading during prepuberty. Interestingly, prepubertal girls who completed 7 months of a drop-jumping program (three times/week) did not demonstrate greater gains in MRI-derived bone strength at the mid-femur compared with girls in the control group [79]. As the jumps were unidirectional, more dynamic loads may have been necessary to elicit an osteogenic response.

Whereas the aforementioned trials all included a specific bone-loading component, the Malmö Pediatric Osteoporosis Prevention (POP) study investigated whether increasing curriculum time for physical education could enhance bone accrual. In this 5-year controlled trial, children in the intervention school (aged 6–9 years at baseline) participated in 40 min of daily physical education (200 min/week) compared with the usual 60 min/week of physical education in control schools. After the first 2 years of the intervention, no differences in bone structure (using

HSA) were observed between intervention and control girls [80, 81]; however, girls in the intervention group gained significantly more lumbar spine and total body BMC and aBMD than control girls [82]. Over the 5-year study period, intervention girls gained significantly more femoral neck BMC and spine aBMD (by DXA), and had 8 % greater cortical area at the tibial shaft and 9 % greater total area at the radial shaft (by pQCT) compared with girls in the control group [83]. Interestingly, the associated 8–13 % greater estimated bone bending strength (SSI_p) at both shaft sites in the intervention group was not significantly different from girls in the control group [83]. Although more robust sample sizes are necessary to confirm these findings, this study suggests that a general exercise program without a specific bone-loading component may enhance bone health in young girls.

School-based intervention trials are challenging to implement and their success depends largely upon participant and teacher compliance. Within the current literature, significant heterogeneity exists across school-based intervention trials regarding the type, intensity, frequency, and duration of the interventions, as well as the imaging tools, scan acquisition, and analysis procedures [12]. Nevertheless, the response to skeletal loading appears to be sex- and maturity specific. Convincing evidence supports the role of high-impact exercise in augmenting skeletal development in pre- and early pubertal girls. Further work is needed to better understand the structural and microarchitectural adaptations to the loads associated with weight-bearing activity including the optimal dose necessary to elicit meaningful benefits.

Observational Studies

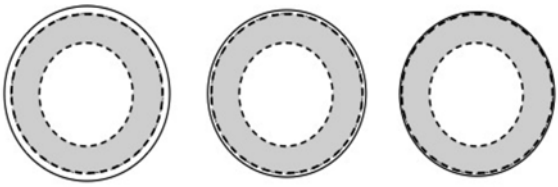
Observational studies, including those of groups of athletes subjected to different loading conditions and of habitual physical activity, represent the largest body of evidence to support the positive association between physical activity and bone health during growth. These studies have traditionally relied on DXA technology, and have shown significant bone mass benefits in children who participate in weight-bearing sports such as gymnastics, tennis, running, and ballet compared with non-athlete groups [84–87]. Similarly, leisure-time physical activity is a significant predictor of bone mass accrual in girls and boys [64, 88]. With increased use of 3D imaging tools, we are now gaining insight into the bone structural advantages that are associated with weight-bearing activity. Thus, in this section we focus on observational studies that employed such tools.

Racquet Sports

Athletes in racquet sports such as tennis and badminton provide a unique model for investigating bone adaptation to loading, as within-subject comparisons of the playing and non-playing arms allows control of confounding factors such as genetics,

hormones, and diet. The seminal cross-sectional DXA study by Kannus and colleagues [84] paved the way for investigations using more sophisticated imaging tools. Side-to-side differences in BMC were compared in the playing vs. non-playing arms of female racquet sport players and controls. Not surprisingly, athletes had significantly greater side-to-side differences compared with controls (3–5 % vs. 9–16 %). However, more interestingly, players who initiated training prior to menarche had side-to-side differences nearly twice that of players who began training after menarche, suggesting that the skeletal benefits of weight-bearing activity are maximized during the premenarcheal years [84].

The bone mass advantage in the playing arm of female racquet sport athletes is also associated with significant bone strength benefits. For example, bone strength (polar second moment of area) measured with MRI at distal and shaft sites of the humerus in young female tennis players was 11–23 % greater in the playing arm than in the non-playing arm [89]. Similarly, side-to-side differences in pQCT-derived BMC, bone CSA, and strength (BSI) at distal and shaft sites of the radius and humerus were significantly greater in female racquet sport athletes compared with controls. As in the Kannus et al. study, the side-to-side differences in bone structure and strength were double the magnitude in women who began racquet sport training prior to menarche compared with women who began training after menarche (Fig. 4.4) [90]. Finally, in the only prospective study of racquet sport athletes conducted to date, 12-month changes in MRI-derived bone geometry



	Side-to-side difference (%)		
	Young Starters	Old Starters	Controls
Total CSA	12.3	5.3	3.4
Cortical CSA	20.0	9.2	3.1
Cortical BMD	-0.8	-0.7	-0.9
Bone Strength (BSI)	26.5	10.2	4.0

Fig. 4.4 Average side-to-side differences in humeral midshaft total bone CSA, cortical CSA, cortical bone mineral density (BMD), and bone strength index (BSI) between the playing and non-playing arm in female racquet sport athletes as measured with peripheral QCT. The *solid line* represents the playing arm (or dominant arm in controls). [Adapted from Macdonald HM, Ashe MC, McKay HA. The link between physical activity and bone strength across the lifespan. Int J Clin Rheumatol; 2009 Aug;4(4):437–63. With permission from Future Medicine, Ltd.]

(total and cortical area) were significantly greater among pre- and peri-pubertal female competitive tennis players compared with postpubertal players [91]. Collectively, these findings support the existence of a "window of opportunity" during pre- and early puberty where the skeleton is particularly sensitive to mechanical stimuli.

These racquet sport studies also suggested that gains in bone structure at shaft sites and distal sites (total and cortical area) during pre- and early puberty were attributed to bone accrual on the outer bone surface (periosteal expansion) as opposed to endosteal apposition [89–91]. In contrast, training initiated after puberty was associated with greater bone apposition on the endosteal surface, conferring little benefit to bone bending strength [89]. These maturational differences in bone adaptation are likely a result of rising estrogen levels throughout puberty, which inhibit resorption on the endosteal surface during rapid growth and promote bone formation in later puberty [92].

Gymnastics

Artistic gymnastics incurs an extremely high mechanical stimulus to the skeleton (ground reaction forces greater than ten times body weight [93]) and thus, provides a unique model for examining the effects of loading on bone. Gymnasts consistently demonstrate greater bone density, structure, and strength in the upper and lower limbs compared with their non-gymnast peers, and a number of studies in recent years have documented these skeletal advantages using pQCT [94–98].

As with racquet sport athletes, substantial adaptation on bone surfaces (estimated by changes in CSA) at shaft sites contributes to greater bone strength in gymnasts. In a cross-sectional study of 5–11 year old prepubertal boys and girls, the 5–7 % greater total and cortical CSA at the radial shaft of elite gymnasts contributed to 9 % greater estimated bone strength (SSI_p) compared with non-gymnast controls [95]. Similar findings were recently reported in 6–11 year old non-elite gymnasts (<16 h/week gymnastics) (Fig. 4.5) [96] and in 4–9 year old recreational current and ex-gymnasts (at least 45 min/week of gymnastics) [97]. Distal sites, on the other hand, demonstrate greater bone strength through adaptations to bone density. Recreational gymnasts and ex-gymnasts demonstrated 6–8 % greater total BMD at the distal radius, which contributed to 22–25 % greater estimated bone strength (BSI) [97]. Collectively, these findings suggest that even recreational gymnastics can provide skeletal benefits in prepuberty.

Benefits to bone structure and strength associated with gymnastics training appear to persist into late adolescence. A small cross-sectional study examined bone strength and structure (by pQCT) in post-menarcheal girls ($n = 16$, mean age 16.7 years) who were ex-gymnasts but had participated in gymnastics (>5 h/week for at least 2 years) throughout early puberty. Ex-gymnasts had 19 % greater trabecular BMD and 25–26 % greater cortical and total CSA at the distal radius, which together conferred 34 % greater estimated bone strength (BSI) compared with non-gymnasts. Similarly, total and cortical CSA were 22–33 % greater in ex-gymnasts

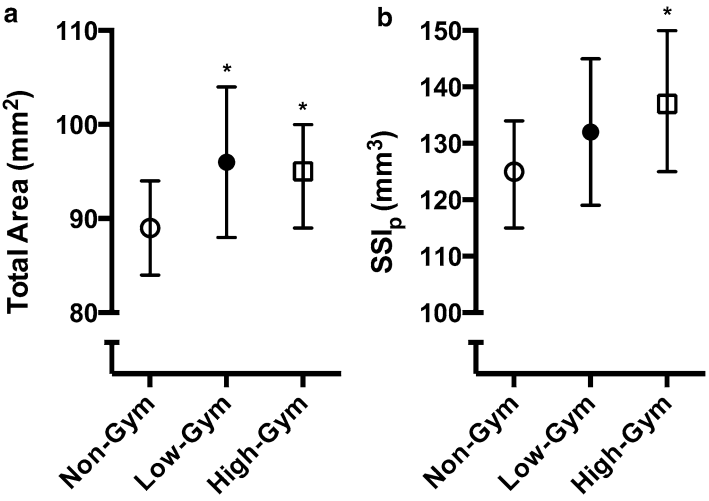


Fig. 4.5 (**a**) Bone structure (total area) and (**b**) estimated bone strength (strength–strain index, SSI_p) at the proximal radius (66 % site) measured with peripheral quantitative computed tomography (pQCT) in prepubertal female non-gymnasts (Non-Gym), low-training volume gymnasts (Low-Gym), and high-training volume gymnasts (High-Gym). *Asterisk* indicates significantly different from Non-Gym. *Bars* represent 95 % confidence intervals (Based on data from [96])

at the radial shaft, and the larger bone area was associated with 46 % greater bone strength (SSI_p) compared with non-gymnasts [98].

While prospective studies investigating the role of gymnastics on bone accrual are limited [85, 99], the Young Recreational Gymnast Study recently demonstrated that recreational gymnasts between 4 and 9 years of age at baseline had 3 % greater total body and 7 % greater femoral neck BMC over 4 years of follow-up compared with their non-gymnast peers [85]. Subsequent analyses in the same cohort using HSA demonstrated that recreational gymnasts also have 3–6 % greater CSA at all three sites of the femoral neck and 6–7 % greater estimated bone strength (section modulus) at the narrow neck and intertrochanter compared with non-gymnasts [94]. Conversely, ex-gymnasts, the majority of whom ceased participation between the first and second measurement, did not demonstrate any advantages in bone parameters compared with non-gymnasts [85, 94]. In summary, participation in gymnastics, whether elite or recreational, is associated with significant bone health benefits in young girls. However, maintenance of the benefits associated with recreational gymnastics appears to be dependent on continued participation.

Leisure-Time Physical Activity

As not all children are engaged in activities such as gymnastics or racquet sports, we must also consider the influence of more general, leisure-time physical activity on bone health. Current physical activity guidelines recommend that children and

adolescents engage in 60 min/day of moderate to vigorous physical activity to achieve health benefits [100, 101]. Guidelines also recommend that children and adolescents engage in muscle and bone-strengthening activities three times/week [100, 101]. While the specific physical activity prescription for optimal bone health is still unknown, the important role of weight-bearing physical activity for shaping skeletal structure throughout the lifespan is well documented.

Similar to the variation in bone imaging procedures discussed previously, there is considerable variation across observational studies in the assessment of physical activity. Measurement techniques range from subjective self-report questionnaires to objective monitoring devices such as accelerometers. Questionnaires are often the tool of choice because they are cost-effective, easy to administer, and are a low burden to the participant [102]. However, self-report questionnaires are subject to recall bias, and while they can provide contextual information regarding physical activity (setting and type of physical activity), questionnaires do not adequately capture physical activity intensity. In contrast, accelerometers can measure physical activity intensity, frequency, and duration. Although accelerometers were originally designed to estimate energy expenditure and not ground reaction forces, strong correlations between ground reaction forces and both accelerometer counts and raw acceleration output suggest they are an appropriate tool for estimating mechanical loads associated with weight-bearing activity [103].

Regardless of physical activity measurement technique, observational studies, both cross-sectional and longitudinal, consistently demonstrate that more active children and adolescents have enhanced bone health and accrue more bone mass and strength compared with their less active peers [36, 37, 64]. For example, vigorous[2] physical activity (derived using accelerometry) was a significant predictor of estimated femoral neck bending and compressive strength (by HSA) in pre- [104, 105] and early pubertal girls [105]. Similarly, 9–13 year old girls in the highest physical activity quintile (via self-report questionnaire) demonstrated 8–9 % greater estimated bone strength and 3–4 % greater outer bone circumference (periosteal circumference) at the tibial shaft and metaphysis (by pQCT) compared with their peers in the lowest physical activity quintile [106]. Finally, prepubertal girls who reported participation in high-impact activity (by questionnaire) demonstrated 7 % greater estimated bone strength (polar cross-sectional moment of inertia, CSMI) and 6 % greater cortical thickness at the tibial shaft (by pQCT) compared with girls who engaged in low-impact activities [107]. While these cross-sectional studies clearly highlight a strong association between weight-bearing activity and bone strength in prepubertal girls, the relationship is less clear in adolescent girls. Two pQCT studies reported no significant associations between self-reported weight-bearing activity or overall physical activity and estimates of bone strength at the tibia and radius [108, 109], while the only HR-pQCT study to date demonstrated a significant relationship between impact physical activity (by questionnaire) and total BMD, trabecular BMD, and trabecular number at the distal tibia in 15–20 year

[2] Six metabolic equivalents (METs).

old girls [110]. There is a need for prospective studies to examine the structural and microarchitectural adaptations associated with physical activity in adolescence.

Whereas the aforementioned cross-sectional studies provide only a snapshot of the physical activity–bone relationship, prospective studies such as the University of Saskatchewan PBMAS allow us to more closely examine the influence of physical activity on normal bone accrual, while controlling for maturation using age at PHV. In their 7-year study, Bailey and colleagues demonstrated that girls in the highest quartile of physical activity (via self-report questionnaire) gained 11–18 % more BMC at the femoral neck, lumbar spine, and total body compared with girls in the lower quartile. In a subsequent analysis of the PBMAS cohort, self-reported physical activity was also a significant predictor of bone CSA and estimated bone strength (section modulus, HSA) at the femoral neck [36, 64]. Interestingly, physical activity was no longer a significant predictor of bone CSA and section modulus once lean mass (surrogate of muscle force) was entered into the multilevel model, suggesting that muscle forces mediate the relationship between bone structure and physical activity [36]. Similar findings were demonstrated in the Iowa Bone Development Study, an ongoing longitudinal study of bone health during childhood, adolescence, and young adulthood. Moderate to vigorous physical activity, assessed by accelerometry, positively predicted bone CSA and strength (section modulus, HSA) from age 5 to 11 [37]. As in the PBMAS, physical activity was no longer a significant predictor of bone outcomes when lean mass was entered into the multilevel model, again suggesting that muscle forces mediate the association between physical activity and bone health. Moving forward, there is a need for longitudinal studies that use HR-pQCT, pQCT, or MRI to examine the influence of habitual physical activity on bone structure and strength.

Triad Populations

Recent reviews highlight that skeletal benefits of weight-bearing exercise may not be conferred to adolescent athletes with menstrual dysfunction [111, 112]. Specifically, athletes engaged in repetitive loading activities such as running and ballet who experience menstrual disturbances often have low aBMD at non-weight-bearing sites (lumbar spine and distal forearm) [113, 114]. Further, bone health in amenorrheic athletes may not only be compromised compared with eumenorrheic athletes, but may also be lower than that of sedentary women [115]. This was illustrated in a DXA-based study of 12–18 year old female endurance athletes and controls in which amenorrheic athletes had 7–10 % lower aBMD at the spine and whole body compared with their eumenorrheic peers and healthy controls [113]. Despite similar LBM across groups, amenorrheic athletes also had 12 % lower aBMD at the hip compared with athletes without menstrual dysfunction [113].

While studies evaluating “catch-up” of bone accrual during adolescence are sparse, Barrack and colleagues followed adolescent endurance runners for 3 years and showed that despite weight gain and greater number of menses per year, 13 of

15 runners with low bone mass at baseline (1 or 2 SD below age- and sex-specific reference data) exhibited low bone mass at follow-up [116]. Nevertheless, two athletes in this cohort demonstrated significant increases in lumbar spine aBMD to within a normal range over the 3-year follow-up [116]. Additional prospective studies are required to evaluate the potential for catch-up during adolescence. Given that the greatest accrual of bone mass occurs in the 2 years around PHV (approximately age 11–13 in girls) [64], decreased bone accrual during adolescence is of great concern for immediate bone fragility and future skeletal health.

DXA-based studies have helped to shed light on bone health issues in athletic populations considered at risk for developing the female athlete triad. As a result, the American College of Sports Medicine now recommends DXA scans in females with oligomenorrhea or amenorrhea, disordered eating or a stress fracture [117]. However, clinicians must keep DXA's limitations in mind when interpreting scans, including the systematic underestimation of aBMD in smaller individuals and the challenges presented by changes in body size and composition.

Recently, disparities between amenorrheic and eumenorrheic athletes have also been uncovered using 3D techniques. Ackerman and colleagues [114, 115] used HR-pQCT to assess bone structure, microarchitecture, and strength in amenorrheic and eumenorrheic endurance athletes and healthy controls aged 15–21 years. While bone structure (bone area at the distal radius and tibia) was similar in both groups of athletes, regardless of menstrual dysfunction status, amenorrheic athletes had lower trabecular number and greater trabecular separation at the distal tibia and lower trabecular density at the radius compared with eumenorrheic peers and healthy controls [114]. Subsequent analyses using finite element analysis identified lower estimated bone strength (failure load and stiffness) in amenorrheic athletes compared with nonathletic controls at the distal radius. Moreover, while eumenorrheic athletes demonstrated a significant bone strength advantage at the weight-bearing tibia compared with nonathletic controls, amenorrheic athletes reaped no such benefits (Fig. 4.6) [115]. These studies suggest that amenorrheic athletes are at a significant skeletal disadvantage compared with their normally menstruating peers. Additionally, weight-bearing exercise may not be able to compensate for the associated detrimental effects of estrogen deficiency. This field of study would benefit from prospective, longitudinal studies of bone health in those with menstrual dysfunction.

Do the Benefits Achieved During Growth Persist into Adulthood?

It is currently unknown whether exercise-related gains in bone structure and strength are maintained into adulthood and associated with reduced fracture risk later in life. Results of elegantly designed animal models support lifelong benefits of exercise during growth on bone structure, strength, and fracture resistance [118]. A similar prospective study has yet to be conducted in humans due to obvious methodological challenges. However, we know that exercise and physical activity engagement

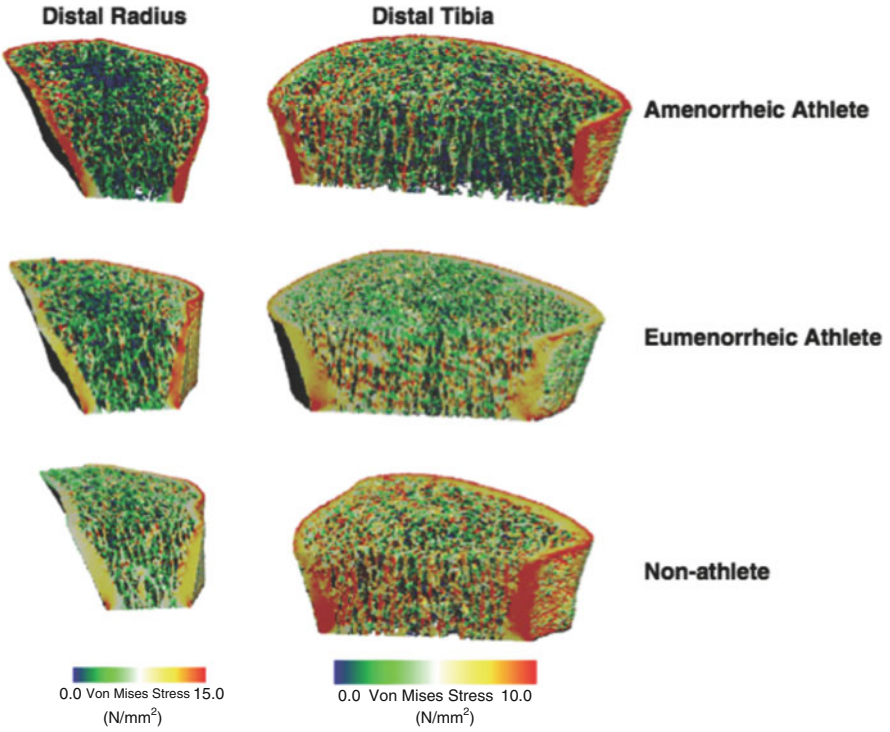


Fig. 4.6 Three-dimensional rendering of distribution of von Mises stresses at the distal radius (*left*) and tibia (*right*) using high-resolution peripheral quantitative computed tomography (HR-pQCT) and finite element analysis in an amenorrheic athlete, eumenorrheic athlete, and non-athletic control. Each bone was subjected to a uniform axial compression of 1,000 N for the distal radius and 1,000 N for the distal tibia. The *colors* indicate the stress levels, with *red* indicating high stresses and *blue* representing low stresses (Reprinted from Ackerman KE, Putman M, Guereca G, Taylor AP, Pierce L, Herzog DB, et al. Cortical microstructure and estimated bone strength in young amenorrheic athletes, eumenorrheic athletes and non-athletes. Bone. 2012 Oct;51(4):680–7. With permission from Elsevier)

during childhood and adolescence predict young adult bone health, as demonstrated in observational [119, 120] and athletic studies [121, 122]. Specifically, results from two key prospective studies, the Penn State Young Women's Health Study (YWHS) and the University of Saskatchewan PBMAS, indicate that girls who were most active during adolescence maintained bone mass and strength advantages over their less active peers in later adolescence and young adulthood. In the YWHS, premenarcheal girls in the most active tertile at baseline (self-report questionnaire; mean age 11.9 years) had 10–11 % greater estimated femoral neck strength (HSA) at age 17 compared with the less physically active girls [119]. Similarly, in a follow-up study of participants in the PBMAS cohort young women and men 23–30 years of age who were most active in adolescence remained more active in adulthood than their peers. Further, those women who were in the upper quartile for physical

activity during adolescence had 9–10 % greater adjusted total hip and femoral neck BMC, 10–12 % greater adjusted cortical bone area and content at the tibia diaphysis and 3 % greater adjusted trabecular content at the distal tibia in adulthood compared with their inactive peers [120, 123].

Skeletal benefits of gymnastics participation during childhood may also persist into later adolescence and young adulthood. For example, women aged 18–36 years who participated in high-level gymnastics during childhood and adolescence had 13–32 % greater cortical and total CSA and 16–25 % greater BMC than women with no previous history of gymnastics training [121]. This contributed to 36–38 % greater estimated bone strength (SSI_p) at shaft sites of the radius and humerus (by pQCT) in former gymnasts compared with women who had never participated in gymnastics [121]. These skeletal advantages were paralleled by 15–18 % greater muscle CSA at the lower and upper arm in the former gymnasts [121]. Benefits of past gymnastics participation were also observed at shaft sites of the tibia and femur, and at the distal tibia, but were smaller in magnitude than those in the upper limbs [121]. More recently, retired elite female gymnasts (10 years post-retirement, aged 22–30 years) demonstrated 10–50 % greater estimated bone strength (BSI and SSI_p; pQCT) at the distal and shaft sites of the radius and tibia compared with non-gymnast controls [122]. Bone strength adaptations in the gymnasts were associated with 15–28 % greater total CSA and BMC (total, cortical and trabecular) at the radius and 9–15 % greater BMC (total, cortical and trabecular) and trabecular BMD at the tibia compared with non-gymnasts.

Finally, the longest follow-up study of a school-based intervention study found that children in the intervention group maintained 1.4 % greater total hip BMC compared with controls 8 years post-cessation of a school-based jumping intervention [124]. Together, these studies suggest that physical activity during childhood and adolescence should be promoted as a means to enhance bone strength not only during growth but also later in life.

The Influence of Exercise on Bone Strength in Young Adult Women

In this section, we review the current literature as it relates to the influence of exercise on bone adaptation during young adulthood.[3] Unlike in childhood and adolescence when bone is rapidly forming, exercise and physical activity in adulthood act to conserve bone health and attenuate bone loss [10]. Much less is known regarding the influence of exercise on bone adaptation in young adulthood. Below we examine findings from exercise intervention studies, athletic populations, leisure-time physical activity studies, and triad populations.

[3]Young adulthood is defined as age 18–40 for this chapter.

Intervention Studies

While studies specifically investigating the effect of exercise on bone health in young adults are sparse, meta-analyses of randomized controlled trials in premenopausal women conclude that impact exercise, nonimpact exercise [125], and high-intensity resistance training are beneficial for lumbar spine aBMD [126], while brief, high-impact exercise is effective for improving hip aBMD [127]. Of the studies included in the most recent review, Kato and colleagues investigated the effect of a 6-month vertical jumping program (ten jumps interspersed by 8–12 s rest, three times/week) in 18–21 year old women [128]. Although bone structure and strength were not assessed in this study, young women randomized to the jumping group experienced a 2–3 % gain in aBMD at the lumbar spine and femoral neck, while no changes were observed in the control group [128]. Likewise, premenopausal women 22–42 years of age who participated in a 6-month unilateral jumping intervention (five sets of ten jumps interspersed with 15-s rest, daily) demonstrated significant gains in femoral neck aBMD, whereas bone mass did not change in the control group or in women who performed the jumps twice per week [129]. The bone mass gains were not accompanied by changes in bone structure or bone strength (by HSA) [129]. It is possible that the osteogenic stimulus of the intervention in the latter study (ground reaction forces two times body weight) and/or the duration of the study were not of sufficient magnitude to elicit bone structural adaptations.

Most recently, Heinonen and colleagues investigated the effects of an 18-month progressive, high-impact exercise intervention (1-h supervised session, including 20-min of jumping and step aerobics, three times/week) on HSA-derived bone structure and strength in an older cohort of premenopausal women (35–45 years) [130]. Women randomly assigned to the exercise group had a significant increase in femoral neck bone area (2.8 %, CSA) and estimated bone strength (3.2 %, section modulus) compared with controls [130]. Despite a trend towards maintenance of increased CSA and bone strength after 3.5 years of detraining, the structural and strength benefits in the intervention group did not persist [130]. These findings highlight that high-impact loading can benefit the skeleton in young and mid-adulthood; however, maintenance of structural and strength adaptations may be dependent on continued participation in weight-bearing exercise.

To our knowledge, only one intervention study has used 3D imaging technology to monitor changes in bone structure and strength in response to exercise. Premenopausal women aged 35–40 years who were randomly assigned to a 12-month supervised, progressive exercise program (60 min, three times/week, bone-loading activities included stepping, stamping, jumping, running, and walking) demonstrated a small but significant increase in bone circumference (0.2 %) at the mid-femur as well as increases in muscle CSA at the mid-femur (1.2 %) and proximal tibia (2.4 %) as measured by spiral QCT [131]. No changes in bone structure were detected in the control group. When the authors conducted additional analyses according to level of participant compliance, they found that the most compliant women (highest quartile of compliance) experienced a 1.2 % increase in bone

circumference and 0.5 % increase in cortical CSA, which contributed to a 2.5 % increase in estimated bone strength (CSMI) [131]. Thus, if bone structure and strength benefits are to be achieved there is a need to encourage participants to comply with the exercise program.

In addition to novel imaging technology, Vainiaonpaa and colleagues [131] incorporated objective monitoring with accelerometers to estimate the impact loading experienced during the study period. Both the volume and intensity of daily impacts, as measured by the accelerometer, predicted 12-month changes in mid-femur bone geometry [131]. Impacts greater than or equal to 1.1 g (i.e., stepping) were associated with changes in CSMI, while impacts greater than 3.9 g (i.e., jumping and running) were associated with changes in cortical thickness [131]. These data suggest that even lower impact activities may benefit the premenopausal skeleton.

Observational Studies

Athletic Populations

As with children and adolescents, adult athletes participating in weight-bearing sports consistently demonstrate improved bone structure and strength compared with their nonathletic peers. For example, female athletes (17–40 years) engaging in high-impact (volleyball, hurdling, triple jump, and high jump), odd-impact (soccer, tennis, squash, and badminton), and repetitive low-impact (running) sports had 11–31 % higher cortical CSA and estimated bone strength (SSI_p, by pQCT) at the tibial shaft compared with athletes engaging in high-magnitude sports (power lifting), nonimpact sports (swimming), and physically active nonathletic controls [132, 133]. Trabecular bone also benefits from weight-bearing activity, as current collegiate female gymnasts (19–22 years) demonstrated 8–14 % higher trabecular number and bone volume fraction (by high-resolution MRI) at the proximal tibia compared with non-gymnast controls [134]. In both of these cross-sectional studies the athletes had been competing in their respective sports for a significant number of years (10–15 years on average). Thus, increased mechanical loading and subsequent bone adaptation likely began in adolescence. As a result, these data may be more indicative of the persistence of bone benefits from adolescence into adulthood rather than of the adult skeleton's ability to adapt to exercise.

While a prospective study would help to answer the question of whether bone adaptations to sporting activity continue in adulthood, a cross-sectional study of pre- and post-menopausal masters track athletes (age 35–94 years) suggests such adaptations do occur. Using pQCT, Wilks and colleagues found that female sprinters who began training after age 20 had 23–26 % greater total BMC, cortical area, and estimated bone strength (SSI_p) at the tibial shaft compared with sedentary controls [135]. Middle-distance and long-distance runners and race-walkers also demonstrated significant bone structure and strength advantages compared with sedentary controls; however, the magnitude of the differences decreased in concert

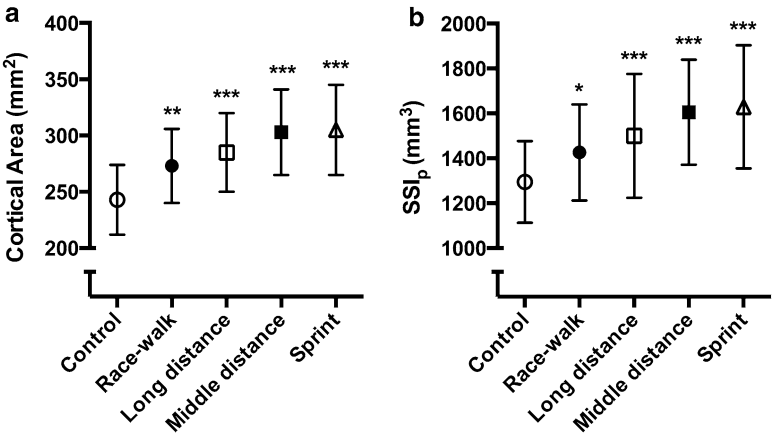


Fig. 4.7 (**a**) Cortical area and (**b**) estimated bone strength (SSI_p) at the tibial diaphysis (38 % site) in adult female runners and control participants. *Asterisks* indicate a significant difference between the control group and the given running group as follows: $*p<0.05$, $**p<0.01$, $***p<0.001$. *Bars* represent mean ± standard deviation (SD) (Based on data from [135])

with decreases in discipline-specific speeds and tibial shaft strains (Fig. 4.7) [135]. While one cannot rule out the possibility that adults with larger and stronger bones self-select into athletics, these data suggest that the musculoskeletal strains experienced by runners are sufficient to induce bone structure and strength adaptations in the mature skeleton.

Leisure-Time Physical Activity

As with studies conducted in athletic cohorts, interpretation of the relationship between leisure-time physical activity and adult bone health is confounded by prior history of physical activity, especially during the growing years. We know that physical activity tracks from childhood into adulthood [136], and that physical activity in childhood and adolescence is an important determinant of physical activity later in life. For example, young adult women who self-reported being highly active in young adulthood had enjoyed physical education during their school years and did not report a decline in physical activity levels between their school years and age 25 [137]. Thus, it is challenging to examine the independent influence of adult physical activity on bone health status in observational studies. Nevertheless, several prospective studies have investigated this issue.

First, a 10-year prospective study of young Finnish women (25–30 years at baseline) demonstrated that women who were more physically active at baseline (via self-report questionnaire) had 7 % greater BMC at the trochanter compared with their less active peers throughout the study period [138]. However, the differences in BMC were not accompanied by any structural or strength (by HSA) differences

between active and inactive women [138]. Although muscle function was measured in this study (leg extension, arm flexion), its influence on bone variables was not assessed. Second, the Penn State YWHS followed adolescent girls from age 12 to 22 years of age [139]. Despite no significant gains in femoral neck aBMD through late adolescence and early adulthood, estimated bone bending strength (section modulus; HSA) significantly increased by 3–5 % with age as a result of continued expansion of the outer bone surface (periosteal expansion) [139]. Both LBM (surrogate of muscle force) and sports participation predicted the changes in bone strength [139]. As postulated by the functional model of bone development [19], these data suggest that the strength of the late adolescent and young adult skeleton is influenced primarily by mechanical loading through lean mass or exercise [139].

Triad Populations

There is convincing evidence that a history of amenorrhea reduces the beneficial skeletal adaptations induced by high-impact training in the mature skeleton [111, 112]. This is illustrated in a recent study by Duckham et al. who investigated bone mass, structure, and strength (DXA, HSA) in endurance athletes and healthy sedentary women 18–45 years of age [140]. Thirty-five percent of the athletes reported current menstrual dysfunction while 40 % reported a history of menstrual dysfunction. Femoral neck aBMD and CSA were 8–11 % greater in eumenorrheic athletes compared with amenorrheic/oligomenorrheic athletes and controls, after adjustment for age, body mass, and height. Further, the amenorrheic/oligomenorrheic group did not demonstrate the greater estimated bone strength compared with nonathletic controls that was experienced by normally menstruating athletes (13 %, section modulus) [140]. The strength index of the femoral neck (ratio of the compressive strength of bone to compressive strength of a fall) was greater in both eumenorrheic and amenorrheic/oligomenorrheic athletes compared with nonathletic controls; however, the magnitude of the difference was lower in those with irregular menses (23 % vs. 14 %). No other differences in bone structure or strength were found between the amenorrheic/oligomenorrheic athletes and healthy controls [140]. Consistent with findings in adolescent girls [115], women with menstrual dysfunction demonstrate reduced bone adaptation to high-impact exercise compared with their normally menstruating peers [140]. Given that femoral neck structure and strength indices in women with menstrual dysfunction were similar to those in nonathletic women, these findings suggest that high-impact exercise may compensate, in part, for the deleterious skeletal effects of prolonged estrogen deficiency. However, it is unclear whether such adaptations are adequate to compensate for the higher bone strains experienced by these individuals.

A history of amenorrhea may also be associated with compromised bone structure and strength in female athletes. For example, former gymnasts without a history of menstrual dysfunction had greater trabecular density and bone strength (BSI) at the distal tibia and radius (by pQCT) compared with healthy controls; however, no such benefits were apparent in former gymnasts with a history of menstrual

dysfunction [141]. Whether this is true at other clinically relevant sites such as the spine at the hip is not yet known.

An important question for the amenorrheic or oligomenorrheic female athlete is whether resumption of normal menses can improve bone health. There is, however, a paucity of literature looking at "catch-up" of skeletal health in female triad athletes. Two case studies that examined former amenorrheic endurance athletes highlight the potential for catch-up of aBMD to within a normal range following resumption of normal menses [142, 143]. Following 6–8 years of reduced training, proper nutrition, weight gain, and resumption of menses in the third decade of life, aBMD increased in both women to within a normal, healthy range [142, 143]. Additionally, a study in female dancers and non-dancers described how seven participants who resumed menses during the 2-year follow-up period experienced a 17 % increase in spinal and wrist aBMD [144]. Despite this catch-up, aBMD remained significantly lower than healthy controls [144]. Similar findings were reported in amenorrheic runners who decreased their training volume and subsequently increased their body weight and resumed menses over 15 months [145, 146]. These studies suggest the potential for catch-up of aBMD, well into the late-20s and early 30s; however, normalization of bone measures likely only occurs following many years of lifestyle changes. This body of research would benefit from investigations exploring whether the improvements in aBMD described in this section are also accompanied by bone structural and strength gains.

Summary and Future Directions

In summary, a large body of evidence supports the important role of exercise in enhancing bone health throughout growth. School-based programs, sporting activities and general, leisure-time physical activity all show promise for promoting bone strength accrual in children and adolescents. Further study in well-defined maturity groups may help to pinpoint the exact window during which the growing skeleton is most responsive to exercise-induced loads. In addition, to elucidate the optimal exercise prescription for bone strength there is a need for well-designed randomized controlled trials that control for important confounding factors such as sex and maturity.

While less data are available for young adults, intervention studies suggest that bone adaptation is also possible in the more mature skeleton. However, in contrast to evidence suggesting sustained skeletal benefits of exercise from adolescence into adulthood, maintenance of exercise-related gains in bone strength achieved during adulthood seem dependent on continued participation in weight-bearing activity. As in studies of children and adolescents, future investigations would benefit from using 3D imaging technology to assess the bone structural and microarchitectural adaptations that underpin exercise-related gains in bone strength.

Irrespective of age, female athletes with irregular menses or a history of menstrual dysfunction are at a significant skeletal disadvantage compared with their eumenorrheic peers. However, as the skeleton demonstrates some capability of catching up

upon resumption of normal menses, female athlete triad populations should be encouraged to adopt healthy eating practices, return to a healthy weight and reduce training loads to regain regularity in their menstruation. Long-term follow-up of triad athletes would help to clarify the most effective remedial approach for bone health. Finally, shifting the focus away from solely bone mass and towards bone strength will ultimately advance our understanding of skeletal health in this population, and aid in the development of effective treatment and prevention programs.

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Chapter 5
Assessment of Bone Health in the Young Athlete

Neville H. Golden

Abbreviations

aBMD	Areal bone mineral density
BMC	Bone mineral content
BMD	Bone mineral density
DXA	Dual energy X-ray absorptiometry
FEA	Finite element analysis
HR-pQCT	High resolution peripheral quantitative computed tomography
vBMD	Volumetric bone mineral density

Introduction

Reduced bone mineral density (BMD) is one of the three components of the Female Athlete Triad, and reduction in BMD or failure to achieve peak BMD, can predispose the athlete to injury, including stress fractures. Assessment of bone health in the young athlete, whose longitudinal growth may not yet be complete and in whom peak bone mass may not yet have been achieved, can be particularly challenging. The aim of this chapter is to describe normal bone acquisition in children and adolescents, and to discuss the advantages and limitations of different methods of assessing bone health in young athletes. Strategies to promote bone health in female athletes are discussed in Chap. 10.

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When the Female Athlete Triad was first described by the American College of Sports Medicine (ACSM) in 1992, the term "osteoporosis" was used to describe the effects of the triad on bone health [1, 2]. With the 2007 revision of the position stand, the term "low BMD" replaced "osteoporosis" [3]. This change in terminology better reflects the spectrum from optimal bone health on the one hand, to osteoporosis at the other extreme. Osteoporosis is a disease of increased bone fragility, characterized not only by low BMD, but also by disturbances in bone microarchitecture; fractures, in turn, can result in pain, deformity, and disability. Reduced BMD precedes osteoporosis and the finding of a low BMD for age provides an opportunity for intervention. While osteoporosis is classically considered a disease of adulthood, it can occur in children and adolescents. Definitions of osteoporosis that have been used for adults have now been refined for use in the pediatric age group.

Normal Bone Acquisition in Children and Adolescents

Bone deposition increases during childhood, accelerates during adolescence, and reaches its peak during the second and third decades of life. Longitudinal studies of measurement of total body bone mineral content (BMC) demonstrate that approximately 40–60 % of peak BMC is accrued during the adolescent years, with 25 % of peak BMC acquired during the 2-year period around peak height velocity [4]. By age 18 years, approximately 90 % of peak bone mass has been accrued [5]. Age of peak bone mass accrual lags behind age of peak height velocity by approximately 6–12 months [4]. This dissociation between linear growth and bone mineral accrual may confer increased vulnerability to bone fragility and may explain, to some degree, the increased rate of forearm fractures in girls between the ages of 8–14 years [6, 7]. Once peak bone mass is achieved, there is a slow, but steady decline until menopause in females, when the rate of decline increases dramatically. With advanced skeletal fragility, even minimal trauma can result in a fracture. In older adults, the risk of osteoporotic fractures increase exponentially with advancing age.

Bone is a metabolically active tissue that comprises a matrix of collagen, hydroxyapatite crystals, and non-collagenous proteins. Deposition of calcium and phosphate on the matrix confers strength to the structure. The axial and appendicular skeleton contain both cortical and trabecular bone. Cortical bone, comprising 80 % of the skeleton, is composed of dense compact layers of lamellar bone and is found primarily in the shafts of long bones of the extremities, as well as in the cranium. Trabecular bone is the spongy bone found in the vertebrae and consists of a network of thin plates traversing the marrow cavities of the skeleton. It comprises only 20 % of the skeleton, but is more metabolically active than cortical bone. Changes in BMD usually become apparent at the spine before changes in other parts of the skeleton because the spine contains more metabolically active trabecular bone compared to cortical-rich sites.

The skeleton constantly undergoes cycles of modeling and remodeling, even after full linear growth has been achieved. During remodeling, bone formation, mediated

via osteoblasts, and bone resorption, mediated by osteoclasts, occur concurrently. Mechanical loading during sporting activities increases bone formation and confers site-specific increases in BMD, depending on the sport. For example, gymnasts and figure skaters have increased BMD at the hip [8, 9], rowers have increased BMD at the spine [10], and tennis players have increased BMD of the dominant forearm compared with the non-dominant side [11]. The process of remodeling is controlled by local cytokines, as well as by circulating hormones including parathyroid hormone, 1,25 dihydroxyvitamin D3, insulin-like growth factor-1, and calcitonin [12]. In young children, the rate of cortical bone remodeling is as high as 50 % per year. Net bone mass depends on the balance between bone resorption and bone formation. Reduced BMD for age can therefore be caused by bone loss but it can also be caused by suboptimal accrual of bone during childhood and adolescence.

Assessment of Bone Health in Children and Adolescents

Assessment of bone health requires a detailed history, comprehensive physical examination, and targeted investigative studies. For female athletes, the history should address each of the three components of the triad. Because genetic factors account for approximately 70 % of the variance in BMD, questions should be asked about a family history of osteoporosis. The athlete should be asked about a prior history of stress fractures, and a history of other medical conditions known to be associated with increased bone fragility. Specific questions should be asked about fractures sustained after minimal trauma. The type, duration, intensity, and frequency of exercise should be determined. A detailed 24-h dietary recall should be obtained to assess energy intake and dietary intake of calcium and vitamin D. Specific questions should be asked about behaviors associated with eating disorders or disordered eating (see Chap. 7). A menstrual history should include age of menarche, date of last menstrual period, and details about episodes of oligomenorrhea or prolonged amenorrhea (see Chap. 3).

Height and weight should be measured, and body mass index (BMI) calculated and plotted on the Centers for Disease Control and Prevention growth charts available at http://www.cdc.gov/growthcharts. Particular attention should be paid to athletes who have fallen off percentiles for height, weight, or BMI. Tanner staging should be performed to evaluate for pubertal delay or interruption.

The outcome variable of most relevance to bone health is fracture risk, but there are very few prospective longitudinal studies assessing fracture risk in pediatric patients and even fewer in young female athletes. Fracture risk depends on skeletal fragility, but also on other factors such as age, body weight, other clinical risk factors, and the force of an injury. Skeletal fragility in turn, depends on BMD, but also on bone size, geometry, microarchitecture, and bending strength. Bending strength is affected by the size of a bone. A bone with a large cross-sectional radius will be less likely to fracture than a smaller bone, even when both bones have the same

BMD or BMC. BMD accounts for approximately 70 % of bone strength, and can be used as a surrogate measure of bone health, recognizing that a low BMD does not necessarily translate to increased fracture risk and that it is possible to have increased fracture risk in the presence of normal BMD.

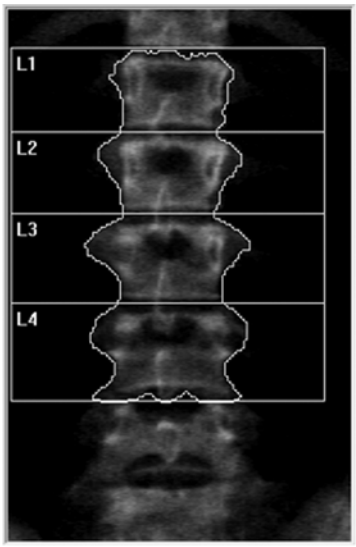
Modalities Used to Assess Bone Health

Dual Energy X-Ray Absorptiometry

The most frequently used method to assess bone mass is dual energy X-Ray absorptiometry (DXA) because of its availability, speed, precision, low cost, and low dose of radiation (5–6 microSievert (μSv) for the lumbar spine, hip and total body, less than the radiation exposure of a transcontinental flight and one tenth that of a standard chest X-ray) [13]. The usual sites measured are the posterior-anterior lumbar spine, hip (femoral neck and total hip), and total body. In children and adolescents, the hip is not a reliable site for measurement of BMD because of variability in skeletal development in this age group which can lead to difficulties in positioning the child or adolescent and resulting in reduced precision of measurements at this site. Therefore, the lumbar spine and the total body are the preferred sites to scan [14]. Scanning time of the spine is less than 1 min and of the total body is approximately 5 min. In addition to measurement of BMD, the total body scan can also assess body composition (fat mass, lean body mass, and percent body fat), information that may be particularly useful for the athlete or athletic trainer.

Bone mass measured by DXA is reported as BMC or BMD. DXA measures the difference in absorption of high-energy and low-energy X-rays as they pass through the body. High density X-rays penetrate both soft tissue and bone, whereas low energy X-rays can only penetrate soft tissue. The difference in absorption of high-energy and low-energy X-rays gives a measure of BMC. Bone mineral density is then calculated from BMC by dividing BMC by the projected area in the coronal plane of the region scanned (Fig. 5.1). This value gives a measure of two-dimensional areal BMD (aBMD, expressed as g/cm^2). Robust pediatric reference databases are now available for children over the age of 5 years and are included with the software of the major DXA manufacturers [15–18].

Based on data in postmenopausal women, a 1 standard deviation (SD) reduction in aBMD is associated with a twofold increase in fracture risk and in adults, osteoporosis has been operationally defined as a BMD $\leq$ 2.5 SD below the young adult mean (T-score ≤ -2.5) and osteopenia as a T-score < -1.0. In children and adolescents, Z-scores (the number of SD below the age-matched mean) should be used instead of T-scores. A low BMD T-score in a 14-year-old athlete who has not yet achieved peak bone mass may be perfectly normal when compared with age-matched controls (Fig. 5.1). In addition, because DXA measures aBMD rather than volumetric density (vBMD, expressed as g/cm^3), it can underestimate true volumetric density in small children and adolescents and overestimate it in larger children and adolescents.



DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T-Score	Z-Score
L1	13.67	9.94	0.727	-1.8	
L2	13.66	11.56	0.846	-1.7	
L3	14.11	12.67	0.898	-1.7	
L4	16.57	14.67	0.886	-2.1	
Total	**58.01**	**48.84**	**0.842**	**-1.9**	**-0.7**

Total DMD CV 1.0%

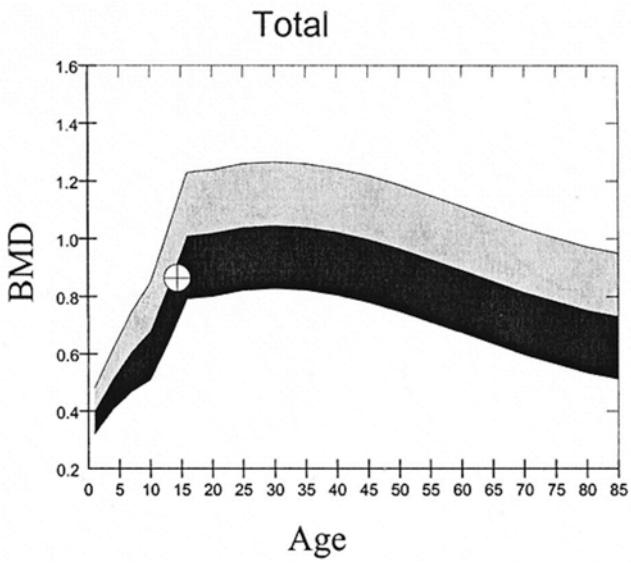


Fig. 5.1 DXA scan of the lumbar spine of a healthy 14-year-old girl. Areal BMD (aBMD) is calculated from BMC by dividing BMC by the projected area in the coronal plane of the region scanned. Despite a low *T*-score, the *Z*-score is normal, implying a normal bone density. In athletes under the age of 20 years, *Z*-scores should be used instead of *T*-scores. Images were obtained with a Hologic QDR-4500 scanner

Furthermore, some female athletes (such a gymnasts and long distance runners) may have short stature or pubertal delay. Correction methods are now available that adjust for height that can improve the accuracy of the BMD *Z*-score [19–21].

Unlike studies in adults in whom a *T*-score in the osteoporotic range is associated with an increased fracture rate, in children and adolescents, there is no specific *Z*-score below which fractures are more likely to occur, but there is a growing body of evidence demonstrating an association between low aBMD and increased fracture risk [22–24]. The International Society for Clinical Densitometry (ISCD) recommends that in males and females younger than 20 years of age, the term "osteopenia" should no longer be used and the term "osteoporosis" should not be based on bone densitometry results alone. The ISCD defines low BMD for chronological age as an age, sex, and body size-adjusted BMD *Z*-score < −2 [14, 25]. The ISCD further recommends that in those under 20 years of age, the diagnosis of "osteoporosis" requires *both* a low BMD or BMC for age (*Z*-score < −2) *plus* a clinically significant fracture, defined as a long bone fracture of the lower extremity, a vertebral compression fracture, or two or more long bone fractures of the upper extremity [25]. Fractures of digits or toes are not included in this definition of a "clinically significant fracture" [26]. Similarly, a child or adolescent with low BMD for chronological age but without a clinically significant fracture does not meet criteria for osteoporosis.

Because bone mass is expected to be higher in athletes than in sedentary individuals, the ACSM recommends that in athletes, a BMD *Z*-score less than −1.0 warrants further investigation, even in the absence of a prior fracture [3]. A recent prospective cohort study of 163 female high school athletes, revealed that a BMD *Z*-score < −1.0 was associated with a 3.6-fold increased risk of musculoskeletal injury (not necessarily fracture) during the interscholastic sports season compared with athletes who had normal BMD values [27]. These findings support the ACSM's recommendations.

Bending strength of a bone depends not only on BMD, but also on bone elasticity and bone geometry. Section modulus, an engineering term used to estimate bending strength of a hollow structure, can be calculated from DXA scans using Hip Structural Analysis, an interactive computer-based program that calculates section modulus from measurements of the cross-sectional area of the femoral neck using images derived from the DXA scan [28]. Section modulus of a large bone will always be greater than that of a smaller bone, even when both bones have the same BMC or BMD. In adults, assessment of bone geometry based on DXA scans is predictive of hip fracture risk, independent of bone density [29, 30]. In young girls, Hip Structural Analysis has been used to demonstrate the positive effects of jumping activities on section modulus of the femoral neck in early pubertal girls [31].

When to Order DXA Scans

There is no strong evidence to guide clinicians when to order DXA scans and a decision to do so for an individual patient still requires clinical judgment. Consensus of expert opinion recommends that DXA scans should be considered in a female athlete with recurrent fractures, a "clinically significant" fracture (defined as a fracture of a long bone of the lower extremity, a vertebral compression fracture, or two or

more fractures of long bones of the upper extremity), a low impact fracture (defined as a fracture sustained from standing height or less), or in an athlete who has been amenorrheic for more than 6 months [26, 32]. Repeat DXA scans should be performed at an interval that can identify a change between the two DXA assessments that exceeds the error of repeated measurements. Based on expert opinion, the ISCD recommends a minimal interval of 6 months before repeating scans [25]. A recent study demonstrated that precision error of DXA scans varies with region of interest, age, and sex. For girls 17 years and younger, a monitoring time interval of 1 year enabled identification of DXA changes that exceeded precision error [33]. Until further information becomes available, for most adolescents and young adults, it is reasonable to repeat the DXA measures after 1 year. The same machine should be used for serial scans in order to make an accurate assessment of the percent change in BMD over the prior year.

Quantitative Computed Tomography

Quantitative computed tomography (QCT) is a three-dimensional imaging modality that accurately measures true vBMD and can differentiate cortical bone from trabecular bone. QTC measurements of the spine and hip are obtained using a clinical whole body scanner that is equipped with special analysis software. Bone size and geometry can be assessed and the scanner can also be used to measure bone density at the distal forearm. QCT machines are costly, not readily available, and utilize high doses of radiation (30–7,000 μSv) [34].

Newer modalities such as peripheral QCT (pQCT) can measure vBMD of the appendicular skeleton with much lower doses of radiation (<3 μSv). The pQCT machines are smaller and more mobile than a clinical whole body scanner and are dedicated to assessment of bone health. Usual sites measured are the non-dominant distal tibia and distal radius. The use of pQCT is particularly appealing for assessment of bone health in athletes because an athlete is more likely to sustain a fracture of the arm or leg than of the hip or spine. In addition to measurement of vBMD, pQCT can measure cortical thickness, cortical density, and trabecular density from cross-sectional images generated. In a cross-sectional study of 204 competitive female athletes using pQCT, Nikander et al. demonstrated that, compared to athletes participating in low impact sports or those in a control group, athletes in high-impact sports had enhanced bone geometry of the tibia evidenced by a thicker cortex at the distal tibia and a greater cross-sectional area of the tibial shaft [35]. A study of 396 Finnish girls aged 10–13 years using pQCT showed that girls who sustained upper limb fractures during puberty had low vBMD of the distal radius at age 10–13 that persisted into adulthood, confirming prior DXA studies regarding the relationship between BMD and fracture risk in children [36].

High resolution pQCT (HR-pQCT) measures small regions of the distal tibia and radius and can evaluate bone microstructure (cortical thickness, trabecular number, thickness, and separation), as seen in Fig. 5.2. It can also be used to estimate bone strength. Scanning time is <3 min and dose of radiation is low (<3 μSv).

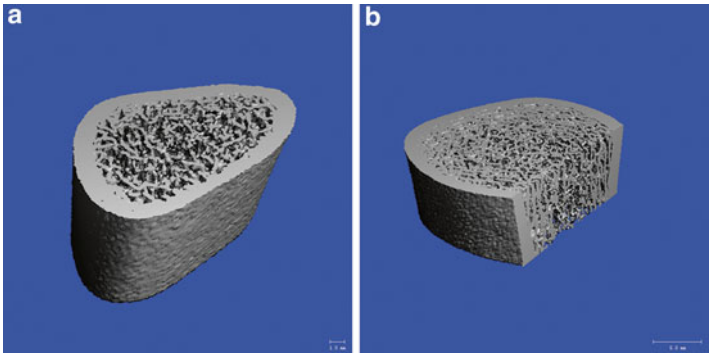


Fig. 5.2 HR-pQCT images of the distal radius (**a**) and distal tibia (**b**) of a healthy 14-year-old girl, demonstrating the trabecular microarchitecture and cortical shell. Images were measured at the 7 % site for the radius and at the 8 % site for the tibia using an Xtreme CT (HR-pQCT) scanner. [Images courtesy of Dr. Melissa Putman and Dr. Catherine Gordon]

Table 5.1 Advantages and limitations of different imaging modalities

	DXA	QCT	pQCT	HR-pQCT
Site measured	Lumbar spine	Lumbar spine	Distal radius	Distal radius
	Hip	Hip	Distal tibia	Distal tibia
	Total body	Distal radius		
Radiation dose (μSv)	5–6	30–7,000	<3	<3
BMD	aBMD	vBMD	vBMD	vBMD
Differentiates cortical from trabecular bone	No	Yes	Yes	Yes
Bone geometry	No	Yes	Yes	Yes
Bone microstructure	No	No	No	Yes

aBMD areal bone mineral density, *vBMD* volumetric bone mineral density, *μSv* microSievert

In postmenopausal women, use of HR-pQCT was better able to predict fragility fractures than measures of BMD performed by DXA [37]. In adolescents, HR-pQCT has been successfully used to assess bone microstructure while avoiding irradiation of the active growth plate [38]. Finite element analysis, FEA, is a computer-based modeling technique used to reconstruct three-dimensional images of the bone in order to estimate bone strength by calculating the predicted load necessary to fracture the bone. Studies using HR-pQCT-based FEA have shown that estimation of bone strength using FEA can enhance prediction of wrist fractures in postmenopausal women [39]. Use of HR-pQCT, while still limited to research, shows great promise for clinical use and has the potential to better predict fracture risk than DXA. Unfortunately HR-pQCT machines are only found in a select few bone research centers. A summary of the advantages and limitations of different imaging modalities is shown in Table 5.1.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a very sensitive method for detecting early stress changes in bone (including stress fractures) and can also provide detailed information about soft tissue injuries (see Chap. 4) [40]. There is no exposure to ionizing radiation but MRI scans are more expensive than DXA scans. MRI is not routinely used as a method of assessment of bone health but is frequently used to evaluate injuries.

Quantitative Ultrasound

Quantitative ultrasound is a noninvasive method of assessing bone health by measuring speed of sound of an ultrasound wave as it is propagated along the surface of bone. Ultrasound measures can be obtained on the calcaneus, tibia, and radius. The machine is easily portable and the test is relatively inexpensive and does not utilize radiation. However, initial enthusiasm for this method has been tempered by poor reliability of measurements, lack of pediatric reference databases, and uncertainty about what skeletal properties are captured by this assessment tool.

Biochemical Markers of Bone Metabolism

Measurement of markers of bone formation and degradation offers an opportunity to assess dynamic changes in bone turnover before these changes become apparent using traditional methods of assessment of BMD or BMC. Osteocalcin (OC) and bone-specific alkaline phosphatase (BSAP) are serum markers of bone formation that are released at different stages of osteoblast proliferation and differentiation. Since OC is incorporated into the bone matrix and is later released into the circulation during bone resorption, it can also be considered a marker of bone turnover. Commonly used measures of bone resorption are Type I collagen C-terminal telopeptide (ICTP), cross-linked C-telopeptide (CTX), and cross-linked N-telopeptide (NTX), which are measured in the serum or urine (Table 5.2). Levels of these markers vary with age and pubertal development. Pediatric reference data are now available for OC, BSAP, CTX, NTX, and ICTP [41]. Bone markers should not be used as a single assessment of bone health, but are best used to monitor dynamic changes over relatively short periods of time, for example for monitoring the response to antiresorptive therapy. Measurement of bone markers is still primarily used in research settings.

Vitamin D Status

Vitamin D is necessary for absorption and utilization of calcium. Individuals with low vitamin D levels are at increased fracture risk. In fact, one prospective study of 6,712 girls aged 9–15 years found that vitamin D intake and not calcium intake was

Table 5.2 Biochemical markers of bone metabolism

Marker	Abbreviation	Sample source
Bone formation		
Osteocalcin	OC	Serum
Bone-specific alkaline phosphatase	BSAP	Serum
Procollagen type I C-terminal peptide	PICP	Serum
Procollagen type I N-terminal peptide	PINP	Serum
Bone resorption		
Deoxypyridinoline	DPD	Urine/serum
Pyridinoline	PYD	Urine
Cross-linked N-telopeptide	NTX	Urine/serum
Cross-linked C-telopeptide	CTX	Urine/serum
Type I collagen C-terminal telopeptide	ICTP	Serum

associated with development of a stress fracture, particularly in those engaging in at least 1 h of high-impact exercise a day [42]. The recommended daily allowance for vitamin D for children and adolescents is 600 IU and the upper daily limit is 4,000 IU [43]. The best method to assess vitamin D stores is measurement of 25 hydroxyvitamin D, 25 (OH) D levels. Measurement of 1-25 dihydroxyvitamin D, 1-25$(OH)_2$ D, the most active form of vitamin D, is not recommended because of its short half-life (approximately 4 h) [44]. According to the Institute of Medicine, a concentration of serum 25 (OH)D > 20 ng/mL (50 nmol/L) is recommended for most healthy children and adolescents [43]. For those with conditions associated with increased bone fragility, serum concentrations of 25 (OH) D above 30 ng/mL are recommended [32].

Summary

Bone densitometry measured by DXA, although not perfect, is the preferred clinical method for assessing BMD and BMC but it is only a surrogate measure of increased bone fragility. Athletes with a normal BMD may sustain a fracture and conversely those with low BMD may not necessarily be at increased fracture risk. DXA measures two-dimensional areal BMD, not three-dimensional vBMD and corrections should be made for size in young athletes. Caution should be exercised in interpreting DXA results in athletes under 20 years of age. BMD *Z*-scores should be used instead of *T*-scores, and the diagnosis of osteoporosis should not be based on DXA results alone. Finally, a DXA measurement is only one part of a comprehensive assessment of skeletal health, which includes a detailed history and comprehensive physical examination. In athletes, HR-pQCT has advantages for assessment of fracture risk because it directly assesses the appendicular skeleton, the most likely part of the skeleton to sustain a fracture in athletes. In addition, HR-pQCT measures true vBMD, differentiates cortical from trabecular bone, and can evaluate bone geometry and

microarchitecture. It can also be used to estimate bone strength. The dose of radiation of HR-pQCT is similar to that of DXA. Although HR-pQCT shows great promise, at the present time, its use is limited to research. Markers of bone formation and degradation can be used to assess dynamic changes in bone health in response to specific interventions, but should not be used as a single assessment of bone health.

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Chapter 6
Neuroendocrine Abnormalities in Female Athletes

Kathryn E. Ackerman and Madhusmita Misra

Introduction

This chapter will review hormonal changes noted acutely and chronically with exercise, specifically focusing on abnormalities noted in female athletes with menstrual dysfunction and/or energy deficiency. Where information regarding amenorrheic (presumably energy deficient) athletes is lacking, hormonal patterns in women with anorexia nervosa have been included. In athletes with functional hypothalamic amenorrhea (FHA), a combination of nutritional deficits, stress, and hormonal aberrations lead to a disruption of gonadotropin-releasing hormone (GnRH) pulsatility, subsequently causing menstrual irregularity or amenorrhea. The last two decades have shed much light on the intricate relationships between exercise, nutrition, appetite regulation, stress, and the reproductive system. Importantly, one of the most severe consequences of FHA is poor bone health. In fact, many hormonal alterations that contribute to FHA also have deleterious effects on bone. This chapter will discuss relationships among the various hormonal changes in FHA and bone metabolism.

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Menstrual Variability

Hypothalamic–Pituitary–Ovarian Dysfunction

As described earlier in this book, menstrual disturbances are common in female athletes and range from subtle disturbances, such as luteal phase defects and anovulation in asymptomatic, eumenorrheic women, to more severe menstrual dysfunction including oligomenorrhea and amenorrhea. Exercise-associated amenorrhea, a form of FHA, is a disruption in hormonal cycling that includes abnormal patterns of GnRH secretion at the hypothalamus. FHA in athletes has been causally linked to decreased energy availability, where caloric intake is inadequate for exercise expenditure, leading to an adaptive suppressive effect on reproduction. Energy is diverted away from the reproductive axis to more vital bodily processes, such as cell maintenance and immune function. Suppression of the hypothalamic–pituitary–ovarian (HPO) axis is coupled with energy-conserving mechanisms [1]. For example, amenorrheic athletes have consistently demonstrated lower resting energy expenditure (REE) than their eumenorrheic counterparts [2, 3].

FHA is a diagnosis of exclusion, and therefore, when assessing an athlete's menstrual status, it is important to keep in mind diagnoses other than FHA [4]. Not all athletes with menstrual abnormalities are in a catabolic state. In a study of 90 Swedish female Olympic athletes from 27 different sporting disciplines, 27 % of those not receiving hormonal contraception reported menstrual dysfunction (i.e., oligo- or amenorrhea) in the previous year. Of the 13 athletes who exhibited menstrual dysfunction based on history and laboratory screening, five were amenorrheic and eight oligomenorrheic. The most common endocrine abnormality in these 13 women was polycystic ovarian syndrome (PCOS), found in one amenorrheic athlete and five oligomenorrheic athletes. This diagnosis was based on history, ultrasound, and clinical or biochemical signs of hyperandrogenism. One athlete was diagnosed with "hypothalamic inhibition" (FHA) and one with hyperprolactinemia. No specific endocrine abnormalities were found in the remaining five athletes with menstrual dysfunction [5]. Thus, while the full differential of menstrual dysfunction in athletes is beyond the scope of this chapter, which primarily focuses on hormonal changes in FHA, it is of utmost importance to consider and rule out other causes of menstrual irregularity, such as pregnancy, thyroid dysfunction, hyperprolactinemia, PCOS, or non-classic congenital adrenal hyperplasia.

Gonadotropin-Releasing Hormone

Gonadotropin-releasing hormone (GnRH) plays a key role in regulating reproductive functioning. It is released by the arcuate nucleus in the hypothalamus in pulses that occur every 60–90 min in the follicular phase and every 120–360 min in the luteal phase of the menstrual cycle, and the precise frequency and amplitude of GnRH pulses is critical for proper HPO axis functioning [6]. The pattern of GnRH pulses coordinates pulsatile release of luteinizing hormone (LH) and follicle-stimulating

hormone (FSH) from the anterior pituitary. LH and FSH subsequently induce production of a variety of hormones including estradiol, progesterone, androstenedione, testosterone, inhibin, activin, and insulin-like growth factor-I (IGF-I).

Aberrations in GnRH pulsatility disrupt secretion of LH and FSH. Abnormal GnRH pulse patterns in FHA include alterations in pulse frequency or amplitude, or both [7]. Many hormones and neurotransmitters can modulate GnRH secretion, indicating that the control of GnRH release patterns is complex. These include the gonadal steroids (with positive and negative feedback effects on GnRH pulsatility), as well as prolactin, corticotropin-releasing hormone (CRH), neuropeptide Y (NPY), catecholamines, and opiates. Some factors, such as CRH and NPY, not only act directly on the hypothalamic GnRH pulse generator, but also on areas that affect caloric consumption and appetite. In turn, appetite-regulating hormones such as leptin, ghrelin, and peptide YY (PYY) can impact GnRH pulsatility, as can hormones such as insulin and IGF-I [8]. Figure 6.1 is a schematic of some of the hormonal interactions in FHA.

Luteinizing Hormone

LH is secreted by gonadotropes in the anterior pituitary and is essential for reproduction. In females, LH is critical for ovulation (the "LH surge"), stimulation of estradiol precursor production (theca cell production of androgens), and maintenance of the corpus luteum. The gonadal hormones released as a result of the coordination of GnRH, LH and FSH, have modulating effects on both the hypothalamus and pituitary. For further details about normal menstrual function, please see Chap. 3.

In a study of 49 adult women with FHA (primary or secondary amenorrhea), the LH secretory patterns over 12–24 h were compared to those during the early follicular phase of normally cycling women. The range of abnormal LH pulses in those with FHA included 8 % apulsatile, 27 % low frequency/low amplitude, 8 % low amplitude/normal frequency, 43 % low frequency/normal amplitude, and 14 % normal frequency/normal amplitude pulses [7]. In comparing 11 pm with 8 am LH secretory parameters of 14–21 year old amenorrheic athletes, eumenorrheic athletes, and eumenorrheic, nonathlete controls, overnight secretory LH pulse height, total pulsatile secretion, and area under the concentration time curve (AUC) were lower in the amenorrheic athletes versus controls [9].

Loucks et al. compared the 24-h patterns of LH pulsatility in eumenorrheic, sedentary women with decreased energy availability from two study-imposed conditions: dietary restriction alone versus dietary restriction and exercise combined. In the exercising group, low energy availability decreased LH pulse frequency by 10 % during waking hours, and increased LH pulse amplitude by 36 % during waking and sleeping hours. The decrease in LH pulse frequency was much less severe than the decrease seen with energy deficiency from diet alone. When energy availability was 45 kcal/kg of lean body mass/day, the stress of exercise did not lower LH pulse frequency nor increase pulse amplitude. This study supports the theory that decreased energy availability is a key component to GnRH and LH disruption in FHA, rather than exercise stress, at least in an acute setting [10].

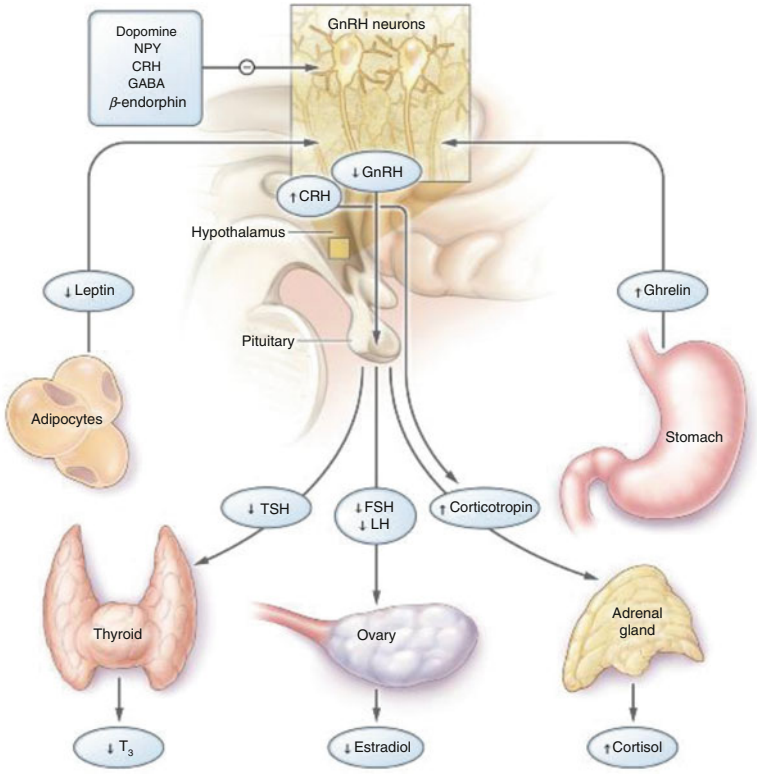

Fig. 6.1 Hormonal and other changes in patients with hypothalamic amenorrhea. In patients with hypothalamic amenorrhea, there are alterations of hormones and other factors that affect the secretion of gonadotropin-releasing hormone (GnRH), including low levels of leptin and high levels of both ghrelin and neuropeptide Y (NPY). B-endorphin, corticotropin-releasing hormone (CRH), dopamine, and **γ**-aminobutyric acid (GABA) are factors that negatively influence GnRH secretion. Some of these factors may also serve as hunger signals from the peripheral to the central nervous system and as links between nutrition and reproduction. Hallmark findings in adolescents and young women with hypothalamic amenorrhea include overactivity of the hypothalamic–pituitary–adrenal axis, suppression of the hypothalamic–pituitary–adrenal axis, and alterations in thyroid hormone regulation. *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *TSH* thyrotropin, and T_3 triiodothyronine. (Reprinted from Gordon CM. Clinical practice. Functional hypothalamic amenorrhea. N Engl J Med. 2010;363(4):365–71, with permission from Massachusetts Medical Society)

Follicle-Stimulating Hormone

FSH, like LH, is produced by gonadotropes in the anterior pituitary and is essential for reproduction. During the early follicular phase of the menstrual cycle, FSH simulates granulosa cells to convert androgens from thecal cells to estradiol, and stimulate folliculogenesis. As inhibin B levels rise, a product of the granulosa cells, FSH production is inhibited and levels fall in the late follicular phase, typically allowing just

one follicle to proceed to ovulation. Toward the end of the luteal phase, progesterone and estradiol concentrations fall, allowing FSH to rise again as the next ovulatory cycle begins. For further details about normal menstrual function, please see Chap. 3.

FSH release is at least partially controlled by GnRH pulsatility. It has been assumed that FSH deficiency acts together with the disruption of LH pulsatility to impair reproductive function in FHA. However, while extensive work has demonstrated abnormalities in LH pulsatility in amenorrheic athletes, changes in patterns of FSH release have not been well elucidated. One study of daily urinary hormonal levels over 3 months in eumenorrheic, recreational runners reported that the elevation in FSH levels during the luteal–follicular transition was lower in athletes with luteal phase defects (shortened luteal phase) versus sedentary and exercising subjects with ovulatory cycles [11]. Over the course of the 3 months, all sedentary controls in this study had consistent menstrual cycle phases, with 90 % of all cycles being ovulatory. However, in the exercising women, only 45 % of cycles were ovulatory, 43 % had luteal phase defects, and 12 % were anovulatory [11].

In a study of patients with FHA versus eumenorrheic controls, only a minority of patients with FHA had a low serum basal FSH level [12]. These lower levels were associated with fewer 6–9 mm follicles in the ovaries, based on ultrasonography. However, despite normal serum FSH levels and normal numbers of 6–9 mm follicles in the majority of the FHA subjects, the functional follicle markers of FSH sensitivity, inhibin B and anti-Müllerian hormone (AMH), were noted to be abnormal, losing some of the correlations to FSH and follicle numbers expected and seen in controls. This suggests that FSH action on the ovary is incomplete and is not accurately reflected by a serum level nor by follicle number noted on ultrasound [12].

Gonadal Hormones

Estrogens

FSH stimulates ovarian production of estrogens by granulosa cells. In addition, estrogens are produced in smaller amounts in adipose tissue, the liver, adrenal glands, and the breasts. Estrogens play important roles in a myriad of physical functions including development of female secondary sexual characteristics, reproduction (by building the endometrial lining and causing the LH surge), sexual desire, coagulation, cardiovascular health, and bone health. While the numerous functions of estrogen are beyond the scope of this chapter, it is important to remember its role in skeletal health, noting that estrogen acts primarily as an antiresorptive hormone, inhibiting osteoclast activity. The greatest accretion of lifetime bone mass is achieved during puberty [13]. Therefore an insufficiency of estrogen during the critical pubertal years can have a profoundly negative effect on a young woman's skeletal health. Estradiol levels in female athletes have correlated highly with lumbar, hip, and whole body BMD in various studies [14]. Please see the following chapters in this book: Chaps. 4, 5, 8, 10.

As with other causes of FHA, it is well established that estradiol levels are lower in amenorrheic athletes compared to eumenorrheic athletes and nonathletes [15, 16]. When 3 months of daily urinary estrone-1-glucuronide (E1G) excretion patterns were studied in women grouped by exercise status (sedentary or exercising) and menstrual status (ovulatory, luteal phase defect, or anovulatory), the variability in estrogen patterns was interesting. There were no significant differences in peak concentrations of E1G excretion among groups. However, the day of the E1G peak was significantly later in exercisers with luteal phase defects compared to exercisers who ovulated. Exercisers with anovulatory cycles had lower E1G excretion in the early follicular phase versus those who were sedentary and ovulatory, and had lower E1G over the entire follicular phase compared to sedentary and exercising ovulators and exercisers with luteal phase defects. During days 6–12, E1G excretion was lower in anovulatory exercisers versus sedentary and exercising ovulators, and the AUC for E1G during the follicular phase was lower, as well. During the luteal phase, E1G AUC was lower in anovulatory exercisers and those with luteal phase defects compared to sedentary ovulating women [17]. Further research is needed to determine the importance of subtle changes in estrogen and other hormone levels in eumenorrheic athletes with luteal phase defects and anovulatory cycles.

While the importance of estrogen for bone health has been established, and there is well-founded concern regarding bone health risks in those athletes with FHA, there have been mixed results in studies assessing the effects of oral contraceptive pills on BMD. Some have shown an increase, some have shown a decrease, and some have found no change in various bone parameters, including BMD [18]. In a study of adolescent girls with anorexia nervosa (AN) and normal weight controls (C), our group found that at baseline, all BMD measures (as assessed by DXA) were lower in AN versus C. When physiologic estradiol replacement and cyclic progesterone was given to some of the AN patients, those who received transdermal estradiol patch had significant increases in spine and hip BMD over the 18 month study [19]. Unlike oral contraceptive pills, estradiol given as a transdermal patch does not suppress IGF-I levels, which is anabolic to bone [20]. Transdermal estrogen studies in Triad patients may help determine if some hormonal replacement in conjunction with improved energy availability could enhance bone health.

Progesterone

Progesterone, or pregn-4-ene-3,20-dione (P4), belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen. P4 is produced by the ovaries, the adrenal glands, and during pregnancy by the placenta. It is stimulated by LH and its effects are enhanced by estrogens. Like all human steroids, P4 is a by-product of cholesterol. In turn, it can then be converted to the mineralocorticoid, aldosterone, and androstenedione, testosterone, estrone, and estradiol [21]. Please see the interrelationships among progesterone, androgens, and estrogens in women in Fig. 6.2.

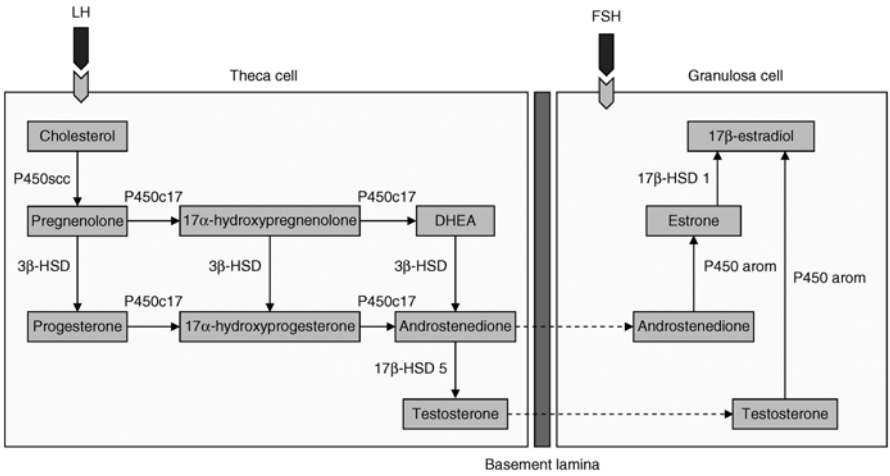

Fig. 6.2 The two-cell, two-gonadotropin hypothesis of ovarian stereoidogenesis regulation. Androgens synthesized by the theca cell diffuse into the avascular granulosa cell compartment. Following stimulation from follicle stimulating hormone (FSH), androstenedione and testosterone are aromatized to estrone and estradiol, respectively. *DHEA* dehydroepiandrosterone; *HSD* hydroxysteroid dehydrogenase; *LH* luteinizing hormone; *P450scc* cytochrome P450 (CYP) side-chain cleavage; *P450arom* CYP P450 aromatase (Reprinted from Enea C et al. Circulating androgens in women: exercise-induced changes. Sports Med. 2011;41(1):1–15, with permission from Springer Verlag)

While it has other small roles in human function, P4 is primarily important for proper menstrual cycle function, fertility, and pregnancy. It is particularly vital for the vascularization and maintenance of the endometrial lining during the luteal phase of the menstrual cycle and throughout pregnancy. In FHA, progesterone levels are reduced. Together with the inappropriately low levels of estradiol, these result in an absence of appropriate follicular development, ovulation, and luteal function [22]. As discussed above, luteal phase defects affect a large proportion of physically active women. Disorders of the luteal phase are characterized by poor endometrial maturation subsequent to inadequate P4 production and short luteal phases, and are associated with infertility and habitual spontaneous abortions [23].

Androgens

The adrenal glands and ovaries produce small amounts of testosterone, but more abundantly secrete weaker androgens. These include dehydroepiandrosterone (DHEA) and its sulfo-conjugate, DHEA sulfate (DHEAS) secreted by the adrenals, and androstenedione secreted by the adrenals and ovaries. These steroids can undergo peripheral conversion to more potent androgens, including testosterone and 5α-dihydrotestosterone (DHT), and can also be converted to estradiol [21].

Testosterone

In a study of women with anorexia nervosa, normal-weight women with FHA, and eumenorrheic controls, total and free testosterone were lower in women with anorexia nervosa than in controls, but subjects with FHA had normal androgen levels. Lower free and total testosterone predicted lower BMD at most skeletal sites measured and free testosterone was positively associated with fat-free mass. After controlling for BMI, total and free testosterone did not remain predictors of BMD [24]. In a small study of bone microarchitecture using flat panel CT in subjects with anorexia and healthy controls, total and free testosterone levels were positively associated with bone volume fraction (the volume of mineralized bone per unit volume of the sample) and trabecular thickness. These associations remained significant after controlling for BMI [25]. Because testosterone can be converted to estradiol, the relationship between testosterone and bone is thought to be mediated through estradiol. In fact, even in a study of male collegiate athletes, estradiol levels were more important determinants of BMD than testosterone [26].

Dehydroepiandrosterone

As mentioned above, DHEA is a steroid produced in the adrenal glands and is a precursor of testosterone, estradiol, and other steroids. Its secretion is largely regulated by ACTH, but angiotensins, gonadotropins, and prolactin may also regulate its production. DHEAS is the hydrophilic storage form that circulates in the blood, but it is converted to DHEA, the principle form used in steroid hormone synthesis. DHEAS concentrations are typically 250–500 times higher in the blood than DHEA. It is the most abundant steroid in circulation, but the extent of its physiological functions is unclear. While it is a clear precursor for various steroids, it has also been found to be a weak agonist and antagonist at testosterone receptors and a stronger agonist at estrogen receptors [27]. There have been contradictory findings in studies regarding DHEAS levels in individuals with anorexia nervosa. Some showed lower concentrations of DHEAS in those with anorexia versus healthy controls [28], higher levels [29], or no difference [24, 30]. In a preliminary study by Oskis et al., salivary DHEA levels were significantly higher in those with anorexia nervosa compared to controls [31]. Gordon et al. found a negative correlation between DHEAS and the bone resorption marker, urinary N-terminal telopeptide (NTX), in adolescent girls with anorexia nervosa [32]. In a recent double-blind, randomized, placebo-controlled trial by DiVasta et al., combined therapy with DHEA and low-dose estrogen/progestin also led to attenuation of bone loss and favorable changes in bone geometry in older adolescents and young women with amenorrhea in the setting of anorexia nervosa [33]. Use of micronized DHEA was safe, and in combination with low-dose estrogen/progestin had beneficial effects on bone health measures in young women with anorexia nervosa. More work is needed to understand the skeletal effects of adrenal steroids in this clinical setting.

Growth Hormone: Insulin-Like Growth Factor-I Axis

Growth hormone (GH), or somatotropin, is a polypeptide synthesized and secreted by the somatotrope cells of the anterior pituitary. Its production is under the control of hypothalamic growth hormone-releasing hormone (GHRH) and somatostatin, as well as ghrelin. GHRH promotes GH gene transcription and translation and increases GH release, while somatostatin has inhibitory effects on GH release. Ghrelin is a GH secretagogue. GH is necessary for overall body growth, including bone growth, but also influences metabolism of carbohydrates, proteins, and lipids. Low blood glucose, sleep, and exercise stimulate the production and release of GH. Alternatively, elevated blood levels of cortisol and glucose decrease its production and secretion. GH effects on growth and metabolism are mostly mediated by IGF-I, a peptide produced in the liver and other tissues in response to GH receptor activation by GH. IGF-I circulates bound to specific proteins, IGF-binding proteins (IGFBPs) and acid labile subunit, which regulate its bioavailability and bioactivity [34]. In addition, GH has direct effects on bone and fat. Both GH and IGF-I are bone anabolic.

In one study, mean serum GH and IGF-I correlated positively with fitness in adolescent girls, but 5 weeks of endurance training led to decreases in IGF-I and IGFBP-5 [35]. Whereas both endurance and resistance exercise have been shown to stimulate acute increases in GH and subsequently IGF-1 [36], decreases in IGF-I and IGFBP-5 over a longer time period in this study were thought to be partially explained by an energy deficit. Studies of anorexia nervosa patients have consistently shown an acquired resistance to GH, with decreased liver production of IGF-I despite elevated GH levels [37]. Low levels of GH-binding protein suggest decreased expression of the GH receptor, possibly accounting for the state of GH resistance during severely decreased energy availability [38]. In addition, IGF-I levels vary with the severity of under nutrition, and correlate positively with body mass index (BMI) and fat mass [39].

Laughlin and Yen [40] found a 70–80 % increase in 24 h mean GH levels in both amenorrheic and eumenorrheic athletes compared to sedentary controls, but with differences in pulsatile patterns. Although pulse amplitude was increased 60 % in eumenorrheic athletes with no change in pulse frequency, amenorrheic athletes demonstrated more frequent pulses and an elevated baseline between pulses. The pattern of GH pulses seen in amenorrheic athletes was associated with a 35 % decrease in GH-binding protein levels, which was not seen in eumenorrheic athletes. In this particular study, levels of IGF-I and IGFBP-3 did not differ in the eumenorrheic or amenorrheic athletes, but IGFBP-1 levels were two- to fourfold higher in the amenorrheic athletes versus the eumenorrheic athletes and controls. This resulted in a threefold reduced ratio of IGF-I/IGFBP-1 in amenorrheic athletes, which likely decreased the bioactivity and hypoglycemic effect of IGF-I [40]. In addition, consistent with other work, LH pulse frequency was related positively with insulin levels and the ratio of IGF-I/IGFBP-1, and negatively with IGFBP-1 concentrations. Overall, amenorrheic athletes displayed evidence of a hypometabolic state, including decreased basal body temperature and reduced levels of

plasma glucose and serum GH-binding protein, a decrease in the IGF-I/IGFBP-1 ratio, accelerated GH pulse frequency, and elevated interpulse GH levels [40].

Few studies have focused specifically on GH pulsatility patterns in athletes with FHA. In one study of five amenorrheic and five eumenorrheic athletes, volunteers participated in two hospital admissions involving a 50 min submaximal exercise bout (70 % maximal oxygen consumption) and an 8 h nocturnal blood sampling period [41]. The amenorrheic athletes demonstrated an increased baseline serum GH level, increased number of nocturnal GH peaks, a prolonged half-life, and more brief GH secretory bursts of decreased mass. The amenorrheic athletes had more disorderly patterns of GH secretion, which paralleled elevated trough concentrations. Both disorderly and elevated trough GH release correlated with blunting of the GH secretory response to acute exercise, seen in the amenorrheic athletes. Concentrations of plasma IGF-I and its associated binding proteins were not significantly different between groups. These findings were different from those reported in patients with anorexia nervosa, who have decreased IGF-I levels, no difference in GH half-life, and increased pulse mass. Results were similar in that both anorexia nervosa subjects and these amenorrheic athletes had decreased regularity of GH pulses and increased pulse frequency [41]. Whether these differences in GH and IGF-I patterns are due to different mechanisms in amenorrheic athletes without eating disorders versus a more severe energy-restricted state, or are simply the result of a small study sample remains to be clarified. Certainly more studies are necessary to better understand GH and IGF-I secretory patterns in female athletes along the menstrual and energy availability spectrum.

Hypothalamic–Pituitary–Thyroid Axis

Thyroxine (T4) and 3,5,3′-triiodothyronine (T3) are tyrosine-based hormones produced by the thyroid gland as a result of thyroid-stimulating hormone (TSH) secretion by the pituitary. TSH secretion is regulated by T3 and T4 negative feedback, as well thyroid-releasing hormone (TRH) secretion from the hypothalamus. The thyroid hormones play critical roles in most bodily functions, including metabolism and bone mineral homeostasis, with T3 being the more metabolically active hormone compared to T4, a precursor of T3. For example, hyperthyroidism increases metabolic rate, decreases bone mineral density, and is associated with increased fracture risk. Hypothyroidism decreases metabolic rate, and while some studies have demonstrated increases in BMD in those with hypothyroidism, bone quality was poor and has been associated with increased fracture risk [42]. T3 is important for local IGF-I secretion in bone, which may account for poor bone quality in patients with hypothyroidism [43].

In a cross-sectional study of hypothalamic–pituitary–thyroid function in amenorrheic athletes versus eumenorrheic athletes and controls, Loucks et al. found lower serum levels of T4, T3, free T4, free T3, and reverse T3 (rT3) in amenorrheic

athletes, and only lower serum T4 levels in eumenorrheic athletes [44]; there were no differences in thyroid-binding globulin or circadian rhythm of TSH secretion. TSH response to TRH stimulation was blunted in amenorrheic athletes versus eumenorrheic athletes, but not compared to eumenorrheic controls [44].

In a subsequent study of the effects of exercise and energy availability manipulations on thyroid function, 46 eumenorrheic, sedentary women were randomly assigned to low intensity exercise, high intensity exercise, or no exercise and low (8 kcal/kg body weight/day) or high energy availability (30 kcal/kg body weight/day) treatments [45]. After 4 days of the various exercise and energy availability regimens, those with low energy availability had 15 % lower T3, 18 % lower free T3, 7 % higher T4, and 24 % higher reverse T3. When energy availability was sufficient, exercise quantity (0 vs. 1,300 kcal/day) and intensity (40 vs. 70 % of aerobic capacity) did not affect the thyroid hormones. Hypothalamic sensitivity to the negative feedback of T3 remained intact, leading to higher levels of T4 in those subjects who were energy restricted. In the energy-deficient groups in this study, T3 levels fell despite sufficient T4 production (precursor of T3), suggesting decreased peripheral deiodinase activity [45]. In a follow-up study of sedentary women divided into groups based on energy availability (10.8, 19.0, 25.0, or 40.4 kcal/kg lean body mass/day) [46], decreases in T3 (16 %) and free T3 (9 %) occurred abruptly when energy availability decreased from 25 to 19 kcal/kg lean body mass/day and increases in free T4 (11 %) and reverse T3 (22 %) occurred abruptly when energy availability decreased from 19.0 to 10.8 kcal/kg fat-free mass/day. No significant changes in total T4 were found [46]. These findings were similar to those noted in anorexia nervosa, where T3 levels are low and reverse T3 levels are elevated [47]. In other studies, exercise and energy restriction have demonstrated increases, decreases, and no change in T4 levels [44–48]. Thus, a further understanding of the interplay of energy and exercise and the hypothalamic–pituitary–thyroid axis is needed.

Hypothalamic–Pituitary–Adrenal Axis

The hypothalamic–pituitary–adrenal (HPA) axis plays a critical role in a person's ability to respond to both emotional and physiologic stress. The hypothalamus secretes corticotropin-releasing hormone (CRH) to trigger the secretion of adrenocorticotropic hormone (ACTH), which stimulates the release of cortisol, a glucocorticoid, from the zona fasciculata of the adrenal cortex. Cortisol has many roles, but primarily functions to alter carbohydrate, protein, and lipid metabolism, increase blood sugar via gluconeogenesis, and suppress the immune system. In addition, it inhibits bone formation, increases bone resorption, decreases calcium absorption, and enhances calcium excretion [49]. In the short-term, stress-induced activation of the HPA axis is adaptive, but chronic exposure of tissues to high cortisol levels secondary to long-term stress may be maladaptive, resulting in adverse effects particularly for bone [8].

Acute intense exercise at or above the anaerobic threshold as well as chronic endurance training have consistently demonstrated activation of the HPA axis and elevated cortisol levels. Studies in individuals exercising at a lower intensity have typically shown minimal if any cortisol response, except when prolonged activity leads to decreased glucose concentration [50]. For example, when subjects performed endurance exercise for 14 h at 50 % VO_2 max, cortisol, ACTH, and CRH responses were unchanged as long as plasma glucose was maintained. The authors suggested a threshold plasma glucose concentration of ≥3.3 mmol/L (59.5 mg/dL) to prevent increases in cortisol [51]. Further work has also clarified HPA patterns with training and overtraining. Short-term intensified training increases both ACTH and cortisol; however, there may be some adaptation with training over time, leading to a reduced response of the HPA axis except when a substantial anaerobic component is present. Conversely, overreaching can lead to an increase in ACTH with a blunting of the adrenal cortisol response, with full-blown overtraining eventually leading to significant under activity of the entire HPA axis and the sympathoadrenal system [50].

Over 20 years ago, Kanaley et al. published a small study involving eumenorrheic athletes in various phases of their menstrual cycles (early follicular, late follicular, and mid-luteal) and amenorrheic athletes. All athletes perform 90 min of treadmill running at 60 % VO_2 max, with blood sampling before and after exercise. Each athlete repeated the testing at different time points. The amenorrheic athletes had higher cortisol levels at rest and greater increases in cortisol in response to exercise than did the eumenorrheic athletes, whose basal and post-exercise cortisol levels were independent of menstrual phase [52]. In a different study of amenorrheic versus eumenorrheic runners, pre-exercise cortisol levels were elevated and cortisol responses to both maximal and submaximal exercise (40 min at 80 % maximal oxygen consumption) were blunted in amenorrheic runners [53]. Perhaps the decrease in cortisol response of amenorrheic runners to exercise in this study was related to overreaching. Further exercise testing studies are needed in amenorrheic athletes to better characterize their response to various levels of activity and training.

In patients with anorexia nervosa, cortisol levels are higher than in normal-weight controls, and are inversely associated with fat mass [54]. Higher cortisol concentrations have also been reported in nonathletic women with FHA versus eumenorrheic controls [16]. Our group specifically examined overnight cortisol secretory parameters in relation to LH pulsatility in 14–21 year old amenorrheic and eumenorrheic athletes and eumenorrheic nonathletic controls. Whereas BMI did not differ among groups, cortisol pulse amplitude, mass, half-life, and AUC were highest in the amenorrheic athletes and were inversely associated with fat mass. There were significant inverse associations between cortisol and LH AUC. Although cortisol concentrations were not associated with levels of bone turnover markers in amenorrheic athletes, cortisol correlated positively with the bone resorption marker, carboxy-terminal telopeptide (CTX), in eumenorrheic athletes, and inversely with the bone formation marker, procollagen type 1 amino-terminal propeptide (P1NP), in nonathletes [55].

Metabolic and Appetite-Regulating Hormones

Insulin

Insulin is a polypeptide synthesized in the pancreas in the β-cells of the islets of Langerhans. It stimulates uptake of glucose from the bloodstream into the liver, skeletal muscle, and adipose tissue, and contributes to cellular growth and hypertrophy. In addition, in vitro, clinical and animal data suggest an anabolic role for insulin in bone. When exposed to physiological doses of insulin, cultured osteoblasts show increased rates of proliferation, collagen synthesis, alkaline phosphatase production, and glucose uptake. Exactly how insulin signaling might promote osteoblastogenesis is yet to be elucidated [56].

While there is a well-characterized increase in glucose transport during exercise, there is also evidence that exercise training decreases insulin concentrations and increases insulin sensitivity [57]. However, when amenorrheic athletes, eumenorrheic athletes, and eumenorrheic nonathlete controls have been compared, hypoinsulinemia was more pronounced in the amenorrheic versus eumenorrheic athletes, extended throughout the day, and was accompanied by reduced glucose increments in response to meals, not observed in the eumenorrheic athletes [40]. When sedentary subjects with ovulatory cycles were compared with recreational runners with ovulatory cycles and those with luteal phase defects, insulin was lower in runners with luteal phase defects compared with the other two groups, similar to insulin decreases observed in amenorrheic athletes and other energy-deprived states [58].

Leptin

Leptin, a cytokine hormone produced by the obesity (ob) gene, is secreted primarily by adipocytes, and binds to leptin receptors, located throughout the body. Leptin is a key messenger of nutritional status and influences appetite, energy balance, and reproduction [59]. Leptin acts directly at the hypothalamus to decrease NPY mRNA and increase POMC mRNA in the arcuate nucleus. NPY is a potent stimulator of food intake, while alpha-melanocyte-stimulating hormone (α-MSH), a cleavage product of POMC, inhibits food intake. In general, leptin decreases when energy is restricted, leading to energy conservation and decreased thermogenesis [60]. Some of the complex interrelationships of leptin and other hormones are depicted in Fig. 6.3.

Athletes have lower leptin levels than sedentary individuals, usually in the context of lower fat mass. However, independent effects of exercise training and increased energy expenditure on leptin, without changes in body fat content, have also been demonstrated [61–64]. It is now more widely held that increased exercise training needs to be accompanied by a state of energy deficit in order to affect leptin levels.

Desgorces et al. [65] found no changes in fasting leptin levels, body weight, percent body fat, or fat mass in rowers after an 8-month training season. Training

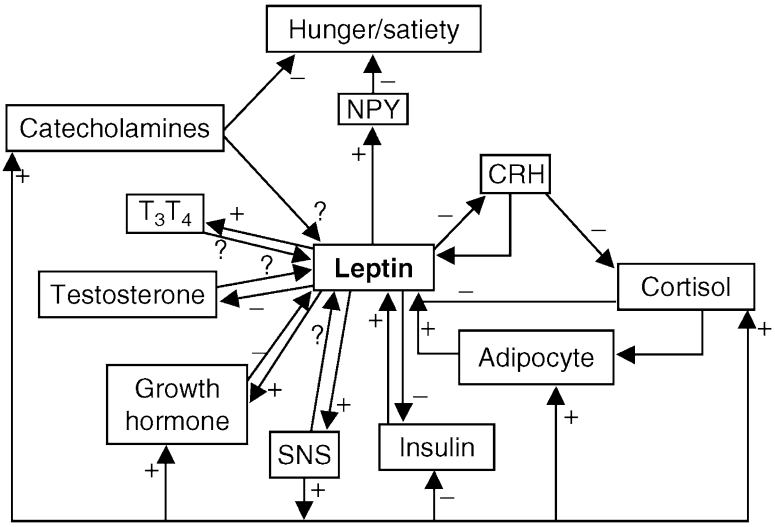

Fig. 6.3 The interrelationship between metabolic hormones, leptin, and hunger. *CRH* corticotropin-releasing hormone; *NPY* neuropeptide-Y; *SNS* sympathetic nervous system; T_3 thyroxine; T_4 triiodothyronine; – indicates pathway inhibits the activity of other homes; + indicates pathway enhances the activity of other hormones; ? indicates relationship has been proposes, but is not proven to exist (Reprinted from McMurray RG, Hackney AC. Interactions of metabolic hormones, adipose tissue and exercise. Sports Med. 2005;35(5):393–412, with permission from Springer Verlag)

volume increased during the 8 months, but so did energy intake, thus maintaining similar body composition. There was a positive correlation between leptin levels and energy availability 24 h after a controlled training session (90 min of ergometer rowing at 70–75 % VO_2 max). After 24 h of recovery, leptin levels were lower when there was decreased energy availability [65]. This correlation between leptin level and energy availability was found regardless of the time during the 8-month training season that the athletes were tested. Further work suggests that leptin levels are only lowered after long-term exercise (≥60 min) or exercise causing energy expenditure ≥800 kcal [66].

De Souza et al. [67] collected fasting morning leptin levels in sedentary ovulatory women, exercising ovulatory women, exercising luteal phase defect/anovulatory women, and amenorrheic athletes (mean age 27.7 ± 1.2 years). Leptin was significantly higher in the sedentary ovulatory women compared to the other three athletic groups, without significant differences in body fat percentage or BMI across groups. However, energy availability was not calculated, and even the exercising ovulatory women may have had sufficiently low energy availability to decrease leptin levels (though not low enough to disrupt ovulation) [67].

In another study, Corr et al. [59] assessed leptin levels in 24 amenorrheic athletes and 26 eumenorrheic athletes (ages 18–30 years). Two fasting morning leptin blood samples were obtained from each subject and pooled. Percent body fat and leptin levels were significantly lower in the amenorrheic athletes versus eumenorrheic athletes,

but the ranges in leptin were similar for both groups. Thus, the modulation of leptin over time, rather than basal measurements, may be more useful in distinguishing menstrual status in exercising women [59].

Hilton and Loucks [68] specifically attempted to tease out the different effects of energy availability and exercise stress on 24-h mean leptin levels and amplitude of the diurnal rhythm of leptin. Healthy, young, eumenorrheic, habitually sedentary women were assigned to sedentary or exercising states, and then studied twice: in a balanced energy availability state (energy intake − energy expenditure = 45 kcal/kg lean body mass/day) and a low energy availability state (energy intake − energy expenditure = 10 kcal/kg lean body mass/day). For the sedentary group, dietary modifications were implemented to achieve energy balance (45 kcal/kg lean body mass/day) or energy deficit (10 kcal/kg lean body mass/day). In the exercising group, low energy availability was achieved by administering a dietary intake of 40 kcal/kg lean body mass/day and an exercise workload of 30 kcal/kg lean body mass/day. In the balanced energy availability condition, dietary energy intake was increased to 75 kcal/kg lean body mass/day to compensate for the same exercise workload.

In random order, the sedentary and exercising women followed the balanced energy availability diet for 4 days and the low energy availability diet for 4 days, both during the early follicular phase of separate menstrual cycles. Low energy availability suppressed 24-h mean leptin and amplitude of leptin, whereas exercise stress did not. Suppression of 24-h mean leptin and amplitude of leptin were more extreme in the sedentary versus exercising women. Carbohydrate availability was defined as the controlled dietary carbohydrate intake administered to each subject minus her carbohydrate oxidation during exercise. Both balanced energy availability treatments provided 1,000 kcal/day of carbohydrate availability, but skeletal muscle altered fuel utilization in response to low energy availability treatment, oxidizing less carbohydrate and more fat during exercise. Therefore, carbohydrate availability was 57 % higher in those whose energy restriction was achieved by exercise versus those whose energy restriction was achieved by dietary restriction. The smaller effect of low energy availability on the diurnal rhythm of leptin in the exercising women may thus be the result of greater availability of glucose to adipose tissue. This study and others support the theory that changes in 24-h leptin levels depend on energy, or carbohydrate availability, not dietary intake, and that exercise has no suppressive effect on the diurnal rhythm of leptin beyond its impact on energy availability [68].

When studying overnight leptin secretory patterns in amenorrheic, eumenorrheic, and nonathletes ages 14–21 years, we found significantly decreased secretory pulse height, secretory pulse mass, total pulsatile secretion, and AUC in the amenorrheic athletes compared to the other two groups. In addition, lower leptin AUC was strongly associated with lower LH AUC, consistent with the known positive effects of leptin on LH pulsatility [9].

Interestingly, leptin has both centrally and peripherally mediated effects on bone. Centrally, mouse models suggest that leptin induces cortical bone formation via β_1 sympathetic activation and/or the GH-IGF-1 axis, but also induces trabecular bone loss via β_2 sympathetic activation [69]. Leptin may also have both positive and negative bone-mediating effects by regulating the expression of various hypothalamic

neuropeptides, including NPY. Peripherally, leptin increases expression of osteogenic genes versus adipogenic genes in bone marrow stromal cells, increases osteoblast proliferation, decreases osteoclastogenesis, and has a positive effect on the appendicular skeleton [70]. Human studies have demonstrated no correlation between BMD and leptin in normal weight children, adolescents, or healthy postmenopausal women, but interventional studies suggest that leptin replacement may positively affect bone health in those with leptin deficiency [70].

Leptin also impacts GnRH secretion and seems to act through interneurons, and likely kisspeptin secretion. Small studies have demonstrated that leptin administration can reverse FHA after a few months of therapy in some adult women, and improve BMD significantly by two years [71, 72]. However, a major side effect of leptin administration is weight loss, limiting the use of leptin as a therapeutic option.

Ghrelin

Ghrelin is secreted primarily by the P/D1 cells in the gastric fundus and is another hormone that reflects energy status. Levels are high in conditions of fasting and hypoglycemia and decrease after food, particularly carbohydrate intake [73]. As with leptin, ghrelin has receptors in the hypothalamus, which are highly expressed in the arcuate nucleus and ventromedial hypothalamus, regions important for food intake regulation [74]. Also like leptin, ghrelin is associated with factors that regulate energy balance and/or indicate energy stores. Ghrelin is thus negatively correlated with BMI, body fat percentage, fat mass, body weight, insulin, T3, and leptin in cross-sectional and longitudinal studies of individuals at the extremes of the weight spectrum: anorexia nervosa and obesity [75–77]. Ghrelin levels are elevated in individuals with anorexia nervosa [77], normalize with weight gain [78], and are lower in obesity [76] and normalize with weight loss [79].

Leidy et al. [75] examined the effects of a 3-month energy deficit-imposed diet and exercise intervention on circulating ghrelin levels in normal-weight, healthy women. Subjects were randomized to study groups that consisted of a control group who performed no exercise and were provided enough calories to maintain initial body weight, and three groups who performed exercise five times a week, but were provided varying quantities of food calories. The three exercising groups consisted of (1) an energy balance group who exercised at a high level and were provided extra calories to maintain body weight; (2) an exercising group who were provided fewer calories than required to maintain initial body weight (moderately energy deficient); and (3) an exercising group who were provided even fewer calories (highly energy deficient). Subjects were regrouped after completion of the intervention into the following three groups: (1) control group (no exercise, weight maintenance diet); (2) weight-stable exercisers (exercised but body weight did not change significantly; and (3) weight-loss exercisers (exercised and lost a significant amount of weight). Maximum weight change observed in the control group was ±1.5 kg, therefore, a decrease in body weight of ≥1.5 kg became the minimum criteria for inclusion into the weight-loss exercising group, whereas exercisers with weight

gain/loss <1.5 kg were included in the weight-stable exercising group. Ghrelin significantly increased over time in the weight-loss group compared with the controls and the weight-stable group. Body weight, body fat, and resting metabolic rate significantly decreased in the weight-loss group before the increase in ghrelin. Thus, even in healthy young women, ghrelin demonstrated similar patterns to those in patients at the extremes of the weight spectrum [75].

De Souza et al. [67] have reported that fasting ghrelin levels are elevated by about 85 % in amenorrheic exercising females, compared to sedentary ovulatory women, exercising ovulatory women, and even luteal phase defect/anovulatory exercisers. This same group examined indices of energy status, including resting energy expenditure and the metabolic hormones, total T3, leptin, and ghrelin across the continuum of energy-related menstrual disturbances in physically active women (recreational and competitive athletes, mean age 24.8 ± 1.4 years) [80]. All groups with menstrual disturbances, including amenorrheic exercisers, anovulatory exercisers, and inconsistent cycle exercisers (a combination of ovulatory, luteal phase defects, and anovulatory cycles over the 2–3 month study period) had significantly lower resting energy expenditure per fat-free mass (REE/FFM) compared with the sedentary ovulatory group.

As reported in prior work by Myerson et al. [81], the exercising amenorrheic group had significantly lower REE/FFM than the exercising ovulatory group [80]. Variability in REE and metabolic hormones were consistent with adaptations to chronic energy deficiency and were distributed across the continuum of menstrual disturbances according to severity (inconsistent cycle exercisers to anovulatory exercisers to amenorrheic exercisers). REE/FFM correlated positively with total T3 and leptin and negatively with ghrelin. This study supports the theory of the Female Athlete Triad as a continuum, demonstrating a dose–response relationship between laboratory measures of energy status (REE, total T3, leptin, and ghrelin) and clinical categories of menstrual dysfunction in female athletes (luteal phase defects, anovulation, and amenorrhea). These data suggest that even subtle changes in energy availability may alter reproductive and endocrine homeostasis in female athletes [80].

In examining younger athletes 14–21 years old, our group found higher fasting ghrelin levels in normal-weight adolescent amenorrheic athletes compared with eumenorrheic athletes and nonathletic controls despite similar activity levels in the two athletic groups [82]. In the same study that examined overnight (11 pm to 7 am) leptin secretory patterns in young amenorrheic and eumenorrheic athletes, and nonathletes, ghrelin sampling (every 20 min) and LH sampling (every 10 min) was also performed. We found significantly higher ghrelin secretory pulse height, secretory pulse mass, total pulsatile secretion, and AUC in the amenorrheic athletes compared with eumenorrheic athletes and nonathletes. As anticipated, there were inverse associations of ghrelin AUC with leptin AUC. In addition, percent body fat was associated positively with leptin secretion and inversely with ghrelin. Secretory pulse height, total pulsatile secretion, and AUC of LH were lower in the amenorrheic athletes versus the nonathletes. Of note, while leptin has positive effects on the HPG axis, ghrelin administration has been demonstrated to inhibit gonadotropin secretion in some animal and human studies [83, 84]. Consistent with these findings, ghrelin AUC was inversely associated with LH AUC, while leptin AUC was associ-

ated positively with LH AUC. Both leptin and ghrelin secretory parameters were associated independently with LH secretory parameters [9]. These data suggest that alterations in hormones that are either secreted (leptin) or regulated by fat (ghrelin) may be a link between low fat mass and altered LH secretion in athletes with amenorrhea.

Peptide YY

PYY is an anorexigenic peptide hormone secreted by neuroendocrine L cells of the distal intestine as a result of caloric intake. Similar to ghrelin, it crosses the blood brain barrier and binds to the Y2 receptor of NPY in the arcuate nucleus in the hypothalamus and inhibits NPY secretion. It also activates proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Through these mechanisms, PYY decreases hunger and food intake. PYY concentrations rise following food intake and remain elevated for several hours. A few days of fasting suppress PYY concentrations by 40–60 % below baseline and PYY infusion during a meal has resulted in decreased food ingestion [85–87].

PYY levels are elevated in patients with anorexia nervosa, exercising women with FHA, and adolescent amenorrheic athletes [2, 88, 89]. PYY concentrations are negatively correlated with BMI and REE [87]. PYY could simply be a marker of energy deficiency or it could help facilitate decreased food intake, exacerbating disordered eating behaviors in those with FHA. Interestingly, the orexigenic peptide ghrelin is elevated in exercising women with FHA, yet so is the anorexigenic peptide PYY. Perhaps PYY contributes to a relative ghrelin resistance in energy-deficient states.

Some animal models have demonstrated a suppressive effect of PYY infusions on reproductive function, decreasing LH release and inhibiting estrous [90, 91]. Utz et al. demonstrated a strong inverse relationship between mean overnight PYY levels and lumbar, hip, and radius BMD in adult women with anorexia nervosa [88]. In a study of adolescent amenorrheic and eumenorrheic athletes and eumenorrheic controls, PYY negatively predicted the bone formation marker, P1NP, as well as lumbar bone mineral apparent density, a surrogate for volumetric bone density [89]. Further research in humans is needed to determine if PYY plays a role in the down-regulation of GnRH and LH pulsatility, along with poor bone health in energy-deficient states, including FHA.

Neuropeptide Y

NPY is a peptide produced by the arcuate and paraventricular nuclei of the hypothalamus, as well as peripherally in the sympathetic nervous system and the pancreas. NPY modulates many metabolic functions, including food intake and reproduction. It acts at the appetite center in the hypothalamus to stimulate feeding

and induces GnRH production if sex steroid concentrations, particularly estradiol, are sufficiently high. In a study of healthy men, intravenous injections of ghrelin led to small, but significant increases in NPY [92]. In hypoestrogenic subjects, NPY has been shown to inhibit GnRH [93, 94].

Patients with FHA have decreased basal concentrations of serum NPY [95]. In one study by Meczekalski et al., subjects with weight-loss-related amenorrhea had lower basal FSH, LH, estradiol, and NPY concentrations compared to controls. When pulsatility of NPY and LH was assessed, the amenorrheic subjects had more frequent NPY and LH pulses [96]. In another study of amenorrheic athletes, eumenorrheic athletes, and sedentary controls matched for BMI, fasting morning leptin and NPY were measured. Notably, body fat mass and percent body fat did not differ between the two groups of athletes, but were significantly lower in both groups of athletes compared to controls. Leptin, with its close relationship to fat stores, was significantly lower in both groups of athletes compared to the controls. Interestingly, NPY was significantly higher in the cycling athletes compared to both the cycling controls and the amenorrheic athletes. Based on these findings and prior work demonstrating a stimulatory effect of NPY on LH release, the researchers hypothesized that NPY could have a protective role in the maintenance of menstrual cycles in some athletes [97]. However, further research is necessary to clarify the impact of exercise on NPY levels.

Adiponectin

Adiponectin is a highly abundant polypeptide secreted by adipocytes. It affects metabolic processes such as glucose regulation and fatty acid oxidation, and unlike other adipokines which are upregulated with increased adiposity, adiponectin concentrations correlate negatively with obesity and insulin resistance [98]. In low weight conditions, conflicting associations have been found between adiponectin and energy status. Adiponectin concentrations have correlated both positively and negatively with weight in anorexia nervosa patients [99]. Because in vitro work demonstrates that visceral fat secretes much greater concentrations of adiponectin than subcutaneous fat, one theory for the variable associations of adiponectin and fat stores is differences in regional fat distribution [100].

Consequences of adiponectin variability in FHA are still being elucidated. In vitro studies have shown that adiponectin suppresses GnRH secretion and activates osteoclasts and osteoblasts [101, 102]. A study of eumenorrheic female rowers both on and off oral contraceptive pills found no significant differences in adiponectin levels in the follicular versus luteal phases of the menstrual cycle. Adiponectin correlated positively with osteocalcin and fat-free mass [103]. O'Donnell and De Souza found that amenorrheic athletes had higher adiponectin concentrations than eumenorrheic athletes and controls, and noted that truncal fat mass was the strongest predictor of log adiponectin adjusted for fat mass. Log serum adiponectin negatively predicted spinal and total BMD. Urinary estrogen AUC trended toward a significant positive association with lumbar BMD, but was not associated with total

BMD. Adiponectin concentrations did not predict urinary estrogen levels. However, log adiponectin and urinary estrogen AUC collectively contributed approximately 37 % to the variability of lumbar BMD. The authors concluded that nutritionally regulated hormones may mediate gonadal status, and that adiponectin and estrogen, together or independently, may affect bone health in amenorrheic athletes [104].

Our group found no differences in adiponectin levels in adolescent amenorrheic athletes versus eumenorrheic athletes and controls, except after controlling for fat mass, but observed a positive relationship between adiponectin and testosterone. Additionally, we found no association between adiponectin and BMD measurements in athletes and controls [89]. In a recent study of adiponectin, BMD, and menstrual function in 80 elite rhythmic gymnasts, salivary adiponectin correlated positively with training intensity, but there was no association with BMD or menstrual status. It must be noted, however, that due to the desire to minimize the stress on athletes (this study was conducted during the 2011 World Championship competition), less than optimal testing methods were used for BMD and menstrual status. BMD was measured using calcaneal ultrasound and menstrual status was determined by questionnaires only [105]. A unifying relationship among adiponectin, energy status, hormonal function, and BMD is yet to be clarified.

Summary

As has been demonstrated by the multiple hormonal changes discussed in this chapter, the individual and combined effects of exercise and energy restriction on the hormonal milieu of female athletes are quite complex. We now know that there are gradations of hormonal modulation in relation to the gradation of energy deficit. In a eumetabolic state, when exercising women have ovulatory menstrual cycles, they may have decreases in total T3 and leptin, as well as increases in cortisol. As they move to a transiently hypometabolic state with possibly luteal phase-deficient menstrual cycles, the alterations in T3, leptin, and cortisol become more severe. In addition, insulin is decreased and growth hormone increases. When energy deficiency leads to a prolonged hypometabolic state with hypothalamic amenorrhea, the above-mentioned hormonal changes are further pronounced in addition to substantial increases in the appetite-regulating hormones ghrelin and PYY, and more severe suppression of the sex steroids. Changes in NPY and adiponectin have been noted, but are still being clarified.

Some of the hormonal changes resulting from FHA are clearly detrimental to reproduction and bone. We know that low estradiol levels are certainly deleterious to both. However, recent findings have suggested that some hormonal changes may be adaptive in an attempt to minimize the energy disruption associated with FHA. Treatment with individual hormonal therapies has yet to demonstrate a large, sustainable, positive impact on menstrual function or BMD. Thus, it is paramount that we continue to investigate how the various hormonal changes, and exercise activity itself, can enhance, rather than hinder the reproductive system and skeleton in order to prevent female athlete triad and improve its treatment.

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Chapter 7
Eating Disorders

Alene Toulany and Debra K. Katzman

Classification and Diagnosis

Three diagnostic categories of eating disorders were described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV TR): anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified [1]. A large majority of young people with clinically significant eating disorders, however, did not meet criteria for these disorders, and were assigned to the residual and heterogenous category, eating disorder not otherwise specified [2].

The focus of the Eating Disorder Work group of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in creating the DSM-5 section on Feeding and Eating Disorders was to create a clinically useful, evidence-based manual for the accurate and consistent diagnosis of eating disorders across the lifespan. As such, the DSM-IV-TR sections on Feeding and Eating Disorders of Infancy or Early Childhood (feeding disorder of infancy or early childhood [FDIC], pica, and rumination disorder) and the section on Eating Disorders were combined into one section called Feeding and Eating Disorders. This new section includes (1) anorexia nervosa; (2) bulimia nervosa; (3) binge-eating disorder; (4) avoidant/restrictive food intake disorder; (5) pica; (6) rumination disorder; (7) other specified feeding or eating disorder; and (8) unspecified feeding or eating disorder.

Feeding and Eating Disorders include several important changes. Overall, the section has taken a lifespan approach to eating disorders, lowered the thresholds of symptom severity, considers behavioral indicators of eating disorder symptoms even in the absence of direct self-report, and uses multiple factors to ascertain symptom profiles [3]. Adoption of these recommendations is believed to allow for

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earlier identification and intervention to prevent the exacerbation of eating disorder symptoms in young people [3].

The major changes that appear in the Feeding and Eating Disorders section of the DSM-5 [4] encompass the recognition of binge-eating disorder as a formal diagnosis, include modest revisions to the diagnostic criteria for anorexia nervosa and bulimia nervosa, eliminate the diagnostic category eating disorder not otherwise specified, and include avoidant/restrictive food intake disorder, previously described in the DSM-IV TR section "Feeding and Eating Disorders of Infancy or Early Childhood" [5]. These changes aim to clarify existing criteria, ensure more accurate diagnoses, and minimize use of the catch-all heterogeneous category, eating disorder not otherwise specified [5].

Anorexia nervosa, which primarily affects adolescent girls and young women, is characterized by distorted body image and excessive and persistent restriction of energy intake that leads to significantly low body weight, in the context of what is minimally expected for age, sex, developmental trajectory, and physical health. Individuals with anorexia nervosa have either an intense fear of gaining weight or persistent behavior that interferes with weight gain despite low weight. The requisite for numeric weight cutoff requirements and requirement for amenorrhea have been eliminated in DSM-5 [2].

Bulimia nervosa is characterized by repeated episodes of binge eating followed by compensatory behaviors (self-induced vomiting; use of laxatives, diuretics, or other medication, including complementary and alternative medications; fasting; or excessive exercise) that are used to counteract weight gain. DSM-5 criteria reduce the frequency of binge eating and compensatory behaviors that people with bulimia nervosa must exhibit, from twice to once weekly.

Binge-eating disorder was officially recognized in DSM-5 as its own diagnostic category of eating disorder. In DSM-IV TR, binge-eating disorder was not recognized as a disorder but rather described in Appendix B: Criteria Sets and Axes Provided for Further Study and was diagnosable using only the catch-all category of eating disorder not otherwise specified [6]. Binge-eating disorder is characterized by recurrent episodes of eating an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances, with episodes marked by feelings of lack of control [6]. Individuals with binge-eating disorder may eat rapidly and until uncomfortably full, even when not physically hungry. Feelings of guilt, embarrassment, and disgust are common along with binge eating alone to hide the behavior. This disorder is associated with marked distress and occurs, on average, at least once a week over three months.

Avoidant/restrictive food intake disorder, previously known as FDIC in the DSM-IV TR, is characterized by persistent failure to meet appropriate nutritional or energy needs and results in one or more of the following: (1) significant loss of weight (or failure to achieve expected weight gain in children); (2) nutritional deficiency; (3) dependence on enteral feeding or oral nutritional supplements; and/or (4) marked interference with psychosocial functioning [6]. This disorder is a broad category intended to capture individuals who substantially restrict their food intake and experience marked physiologic or psychosocial problems but do not

meet criteria for a feeding or eating disorder [2, 7]. The energy and/or nutritional needs in a patient diagnosed with ARFID are not the result of the lack of available food or a culturally sanctioned practice. Further, the diagnosis of ARFID cannot be made if the adolescent has abnormalities in the way in which they perceive their body weight or shape. Finally, it is not explained by another medical or mental disorder that, if treated, the eating problem will go away. For example, some young people may avoid eating solid food after a gastrointestinal illness and develop significant nutritional problems [2]. Extreme and persistent picky food preferences during childhood leading to clinically significant problems are also captured by the ARFID category [2].

A recent study has shown that the DSM-5 diagnostic criteria have good reliability for anorexia nervosa and bulimia nervosa, and acceptable reliability for binge-eating disorder. Further research on the reliability, validity, and clinical utility are needed for all diagnostic categories [8].

Epidemiology

Published epidemiologic data on eating disorders predate the DSM-5 changes. Therefore, this chapter focuses on the available epidemiologic data prior to these changes. The changes in the DSM-5 will result in new epidemiologic data, resulting in a higher incidence and prevalence of anorexia nervosa, bulimia nervosa, and binge-eating disorder. Eating disorders have peak onset during adolescence, with a reported incidence of anorexia nervosa of 109/100,000 in 15–19 year olds [9]. While the overall incidence rate of anorexia nervosa in adults has remained stable over the past decades, there has been an increase in the high-risk group of 15–19-year-old girls [9, 10]. It is uncertain whether this finding is due to earlier detection of anorexia nervosa or an earlier age at onset [10]. The incidence of eating disorders under the age of 13 has been estimated between 1.1 and 2.6/100,000 in three nationally representative pediatric surveillance studies in Canada, Australia, and United Kingdom [11–13]. Eating disorders have also been reported in association with several chronic illnesses and disabilities, in particular type 1 diabetes mellitus [14, 15].

The lifetime prevalence of eating disorders in adults is about 0.6 % for anorexia nervosa, 1 % for bulimia nervosa, and 3 % for binge-eating disorder [16, 17]. Women are more affected than are men [16]. Eating disorders have been reported in both developing and developed nations [18–20]. An increasing occurrence of eating disorders in non-Western societies has been associated with cultural transition and globalization [21–23]. Individuals with eating disorders have significantly elevated mortality rates, with the highest rates occurring in those with anorexia nervosa [24]. The mortality rate from anorexia nervosa is estimated at 5.9 %, the highest rate of mortality among all mental disorders [25]. Comorbid psychiatric conditions are also highly prevalent in individuals with eating disorders [16, 17]. Despite the magnitude, many individuals with eating disorders do not seek treatment [16].

Recent studies have reported that the prevalence of avoidant/restrictive food intake disorder in tertiary care pediatric eating disorders program range from 5 to 14 % [26, 27]. Additional studies from community-based samples are needed.

Pathogenesis and Etiology

Research into the pathogenesis of eating disorders has focused mainly on anorexia nervosa and bulimia nervosa. The causes of eating disorders are complex and include biological, hormonal, psychological, and environmental components. The heritability of eating disorders is similar to that of other psychiatric conditions [28]. Twin and family studies estimate heritability ranges between 50 and 83 % for anorexia nervosa, bulimia nervosa, and binge-eating disorders [29–31]. Hence, considerable genetic influences on the etiology can be assumed for eating disorders [32, 33]. Molecular genetic studies have identified genes and chromosomal regions that may contribute to the development of an eating disorder [34–37].

Many of the biological findings in eating disorders are a result of starvation and malnourishment. However, some are causally linked as risk or maintaining factors [38]. The brain is particularly vulnerable to the consequences of poor nutrition. Alterations in brain structure, metabolism, and neurochemistry have been identified in malnourished and emaciated individuals with anorexia nervosa [39–42]. Alterations in brain metabolism and atrophy have also been reported in bulimia nervosa [43, 44]. These changes are associated with many behavioral and psychosocial disturbances such as rigidity, emotional dysregulation, and social difficulties [38]. Although many symptoms resolve with weight gain, disturbances in brain circuits modulating appetite, mood, cognitive function, and impulse control may persist after recovery from an eating disorder [45–47].

Environmental influences may also contribute to the risk of developing an eating disorder. For example, high-concern parenting in infancy may be associated with the later development of anorexia nervosa [48]. Perinatal complications and premature delivery may also increase the risk of development of an eating disorder by epigenetic mechanisms or damage to the brain from hypoxia [49]. The idealization of thinness in some developed societies encourages dieting and weight-control practices. Mass media propagate a slender ideal that elicits body dissatisfaction [50]. Girls who are obese, experience early puberty, criticism, teasing, and bullying are at increased risk of developing an eating disorder [51–53]. Personality traits such as perfectionism, concerns over self-control, sensitivity to rejection, and low self-esteem have also been implicated. Some sports, such as cheerleading, figure skating, gymnastics, dance, and long distance running, may promote weight loss or thinness, thereby encouraging an eating disorder to develop. Risk factors for eating disorders are summarized in Table 7.1 [52, 54–56].

Table 7.1 Potential risk factors for the development of an eating disorder

1.	Age and female gender
2.	Early childhood eating problems
3.	Childhood obesity or overweight
4.	Weight related teasing of the child/adolescent
5.	Dieting
6.	Perinatal adverse events (prematurity, small for gestational age, cephalohematoma)
7.	Personality traits such as perfectionism, anxiety, low self-esteem, obsessionality
8.	Early puberty
9.	Chronic illness
10.	Physical and sexual abuse
11.	Family history of psychiatric illness, eating disorder, or obesity
12.	Competitive athletics i.e., gymnastics, ice skating, ballet, wrestling
13.	Overanxious parenting

Based on data from [52, 54–56]

Assessment

Primary care clinicians play an important role in the initial detection, evaluation, and progression of eating disorders. Early detection and management of an eating disorder may prevent or lessen the medical complications and psychological consequences associated with starvation and progression of the illness [57, 58]. Primary and secondary prevention is achieved by screening for eating disorders as part of routine annual health care, providing ongoing monitoring and documentation of weight and height on growth charts, and paying careful attention to the signs and symptoms of an early eating disorder [58]. Screening questions regarding eating patterns and body image that can be used for all adolescents and young adults presenting for routine health care are shown in Table 7.2. In addition, the SCOFF screening questionnaire, although not validated in children and adolescents, can provide a framework for screening (Table 7.3). A recent meta-analysis has shown this to be a very useful screening tool [59].

Concern with weight and body shape is extremely common during adolescence [60, 61]. A significant number of pre-adolescents may also have a desire to be thinner [62, 63]. Canadian, American, and Australian cross-sectional data suggest that more than one in five teenagers are "on a diet" at any given time [60, 62, 64, 65]. Approximately 40–66 % of teenage girls and 20–30 % of teenage boys have attempted dieting in the past [66]. Any evidence elicited on history or physical examination of dieting, excessive concern with weight or shape, weight loss or failure to gain weight as expected for age and developmental stage requires further attention. Careful assessment for the possibility of an eating disorder and close monitoring at intervals as frequent as every 1–2 weeks may be needed until the situation becomes clear [58].

Table 7.2 Screening questions that may help to identify an eating disorder at a routine health care visit

What is the most/least you ever weighed? How tall were you then? When was that?
What is your ideal weight?
What do you do for exercise? Level of intensity? How stressed are you if you miss a workout?
Ask for specific dietary practices:
• 24-h diet and fluid history?
• Calorie counting, fat gram counting? Taboo foods? Restrictions?
• Early satiety, bloating, reflux?
• Any binge eating? Frequency, amount, triggers?
• Purging history?
• Use of diuretics, laxatives, diet pills, ipecac?
• Any vomiting? Frequency, how long after meals?
Menstrual history in females: age at menarche? Regularity of cycles? Last menstrual period?
Any history of depression, anxiety, suicidal ideation or attempts?
Use of cigarettes, drugs, alcohol? Sexual history? History of physical or sexual abuse?
Family history: obesity, eating disorders, depression, other mental illness, substance abuse by parents or other family members?
Review of symptoms:
• Dizziness, syncope, weakness, fatigue?
• Pallor, easy bruising or bleeding?
• Cold intolerance?
• Hair loss, lanugo, dry skin?
• Vomiting, diarrhea, constipation?
• Fullness, bloating, abdominal pain, epigastric burning?
• Muscle cramps, joint paints, palpitations, chest pain?
• Symptoms of hyperthyroidism, diabetes, malignancy, infection, inflammatory bowel disease?

Based on data from [58, 70]

Table 7.3 The SCOFF questions[a]

Do you make yourself **S**ick because you feel uncomfortably full?
Do you worry you have lost **C**ontrol over how much you eat?
Have you recently lost more than **O**ne stone in a 3-month period?
Do you believe yourself to be **F**at when others say you are too thin?
Would you say that **F**ood dominates your life?

[a]One point for every "yes"; a score of ≥2 indicates a likely case of anorexia nervosa or bulimia nervosa

Possible findings on physical examination are detailed in Table 7.4. In addition, when an adolescent is referred to their clinician because of concerns raised by parents, friends, or school that he or she is displaying evidence of an eating disorder, it is most likely that the adolescent does have an eating disorder [58]. These concerns should be taken very seriously even if the adolescent denies all symptoms.

Initial laboratory investigations in an eating disorder evaluation should include a complete blood count and differential, platelet count, electrolytes (including calcium, phosphate and magnesium), glucose, liver function tests, thyroid-stimulating

Table 7.4 Possible findings on physical examination in patients with eating disorders

Bradycardia
Hypotension
Hypothermia
Cardiac murmur (mitral valve prolapse)
Dull, thinning scalp hair
Sunken cheeks, sallow and dry skin
Lanugo hair
Atrophic breasts (postpubertal)
Atrophic vaginitis (postpubertal)
Pitting edema of extremities
Emaciated, may wear oversized clothes
Flat affect
Cold extremities, acrocyanosis
Parotitis
Russell's sign (callous on knuckles from self-induced emesis)
Mouth sores
Palatal scratches
Dental enamel erosions

Table 7.5 Differential diagnosis of eating disorders

• Gastrointestinal: inflammatory bowel disease, celiac disease, malabsorption
• Endocrine: hyperthyroidism, diabetes mellitus, Addison's disease, hypopituitarism
• Rheumatologic: systemic lupus erythematosus
• Neurologic: central nervous system lesions (hypothalamic or pituitary tumors)
• Infections: tuberculosis, HIV
• Malignancy: leukemia, lymphoma, brain tumor
• Other: collagen vascular disease, cystic fibrosis
• Psychiatric disorders including mood disorders, anxiety disorders, somatization and psychosis

hormone, erythrocyte sedimentation rate, and urinalysis. Markers of nutritional status (albumin, vitamin D, folate, vitamin B12, iron, and other minerals) may also be considered. Additional tests (urine pregnancy, luteinizing and follicle-stimulating hormone, prolactin, and estradiol) should be considered in patients who are amenorrheic or have delayed puberty. An electrocardiogram should be performed on all patients. Bone densitometry should be considered in those females who are amenorrheic for more than 6 months [67]. Other tests such as echocardiogram, upper gastrointestinal tract series, or brain imaging should be considered in select circumstances as guided by the history and physical examination. For example, magnetic resonance imaging and neuropsychological assessment may be needed for patients with atypical features, such as hallucinations, delusions, delirium, and persistent cognitive impairment, despite weight restoration [68]. Normal laboratory investigations in patients with eating disorders do not exclude serious illness or medical instability. A broad differential diagnosis for the adolescent with symptoms of an eating disorder should always be considered (Table 7.5).

Medical Complications

Eating disorders in adolescents and young adults can cause *serious* medical complications in every organ system (Table 7.6) [42, 58, 69]. The medical complications occurring in individuals with an eating disorder are largely related to the effects of starvation, malnutrition, and weight-control behaviors such as vomiting and laxative abuse. The consequences of nutritional deprivation and metabolic impairment on the growing and developing adolescent body also depend on the length, severity, and number of episodes of restriction and, the timing of those episodes in relationship to normal periods of growth and physical development [70, 71].

Although many of the medical complications improve with nutritional rehabilitation and recovery from the eating disorder, some are potentially irreversible [42]. If the eating disorder occurs before the closure of the epiphyses, growth retardation may become potentially irreversible [72–76], resulting in failure to achieve expected adult height. Other potentially irreversible medical complications in adolescents include loss of dental enamel with chronic vomiting [77]; structural brain changes [39, 78]; pubertal delay or arrest [79]; and impaired acquisition of peak bone mass with an increased fracture risk secondary to low bone mineral density [80–83].

Table 7.6 Medical complications resulting from eating disorders

Medical complications from purging
1. Dehydration and electrolyte imbalance (hypokalemia; hypophosphatemia); hypochloremic alkalosis
2. Use of ipecac: irreversible myocardial damage
3. Chronic vomiting: esophagitis; dental erosions; Mallory-Weiss tears; rare esophageal or gastric rupture
4. Use of laxatives: metabolic acidosis; increased blood urea nitrogen concentration; hyperuricemia; hypocalcemia; hypomagnesemia; chronic dehydration
5. Amenorrhea (can be seen in normal or overweight individuals with bulimia nervosa); menstrual irregularities
Medical complications from caloric restriction
1. Cardiovascular: Electrocardiographic abnormalities: low voltage (sinus bradycardia, T wave inversion, ST segment depression, prolonged corrected QT interval); dysrhythmias include supraventricular beats and ventricular tachycardia; pericardial effusions; congestive heart failure; sudden death; mitral valve prolapse; orthostatic hypotension or tachycardia
2. Gastrointestinal: delayed gastric emptying; slowed gastrointestinal motility; constipation; bloating; hypercholesterolemia; abnormal liver function tests; fatty liver; superior mesenteric artery syndrome; gallstones
3. Renal: increased blood urea nitrogen concentration (from dehydration, decreased glomerular filtration rate) with increased risk of renal stones; total body sodium and potassium depletion caused by starvation; peripheral edema; urinary incontinence
4. Hematologic: leukopenia; anemia; iron deficiency; thrombocytopenia
5. Endocrine: euthyroid sick syndrome; amenorrhea; hypercortisolism; hypercholesterolemia; hypoglycemia; pubertal delay; impaired linear growth; low bone mineral density
6. Neurologic: cortical atrophy; seizures (secondary to metabolic derangements); cognitive deficits

Based on data from [42, 58, 69]

Eating disorders are life-threatening illnesses. At least one-third of all deaths in adults with anorexia nervosa are due to cardiac complications [84–86]. Cardiac abnormalities are often present in the early stages of the eating disorder and may be reversible with prompt identification and treatment [87–89]. Common cardiovascular complications include electrocardiographic abnormalities such as sinus bradycardia, decreased voltage and prolonged QTc, orthostatic hypotension, increased vagal tone, poor myocardial contractility, mitral valve prolapse, reduction in left ventricular wall thickness and mass, and silent pericardial effusion [42, 69, 87–92]. Sinus bradycardia is present in 35–95 % of adolescents with anorexia nervosa, and is believed to be due to the reported increased vagal tone and decreased metabolic rate [42, 69, 91, 92]. Electrocardiographic abnormalities may also be due to other secondary causes such as metabolic and electrolyte disturbances, illicit drugs, medications, or complementary and alternative therapies [42].

Cardiovascular complications occur not only in the initial stages of the disorder but also during refeeding. Refeeding syndrome is a term that refers to various metabolic abnormalities that occur in severely malnourished patients following carbohydrate administration [93, 94]. Clinically, refeeding syndrome consists of a constellation of cardiac, hematological, and neurological symptoms. It has been reported in 6 % of hospitalized patients and can include congestive heart failure and pedal edema, a prolonged QT interval with arrhythmia, tachycardia, and sudden cardiac death [68, 89]. Although multiple organ systems may be involved, cardiac and neurologic dysfunction has been noted in those most severely affected [94]. Hypophosphatemia, a potentially life-threatening complication, is recognized as the biochemical hallmark for refeeding syndrome [95]. Refeeding hypophosphatemia has been associated with the degree of malnutrition [96]. Other electrolyte derangements (i.e., hypokalemia, hypomagnesaemia, hypocalcemia) may also occur and generally result from transcellular shifts of fluid and electrolytes as well as total body depletion [95]. Electrolyte disturbances require immediate attention.

The major endocrine abnormalities associated with eating disorders include hypogonadotropic hypogonadism, hypercortisolemia, hypoglycemia, growth hormone resistance, impaired linear growth, and sick euthyroid syndrome [97, 98]. The clinical manifestation of dysfunctional hypothalamic–pituitary–ovarian axis is amenorrhea and pubertal delay [69]. Development of a low bone density is a serious complication in adolescents with eating disorders, as adolescence is a critical period for the attainment of peak skeletal mass [42]. The pathogenesis of bone loss is associated with impaired bone formation and increased bone resorption, hypoestrogenemia, decreased levels of IGF-1, low dehydroepiandrosterone (DHEA) concentrations, increased cortisol levels, physical activity, poor nutrition, reduced leptin levels, low calcium and vitamin D intake, and low body mass [42, 99]. Weight restoration and the resumption of menses is the safest and most effective way to increase bone mineralization in adolescents with anorexia nervosa [80, 100]. Oral estrogen–progesterone combination pills have not been proven to be effective in increasing bone mineral density. Recent data suggests that physiologic estrogen in the form of the transdermal patch in older girls (bone age >15 years) increases spine and hip bone mineral density. However, complete catch-up in bone mineralization did not occur [101].

In addition, a prospective, randomized controlled study using oral micronized DHEA and estrogen–progesterone combination pills prevented bone loss in young women with anorexia nervosa compared to the decrease in areal BMD in women receiving a placebo [102]. Although most of the endocrine changes that occur in anorexia nervosa represent physiologic adaptation to starvation, some may persist after recovery [97, 98].

Alteration in renal function manifesting as abnormal blood urea nitrogen, decreased glomerular filtration rate, hematuria, and proteinuria have been described in patients with eating disorders [69]. Urea and creatinine are generally low and normal concentrations may mask dehydration or renal dysfunction [103]. Further, 17 % of adolescents with anorexia nervosa have been shown to have nocturnal enuresis, which is thought to be related to decreased functional bladder capacity and detrusor instability [104].

Serum pH and electrolyte abnormalities are common and result from starvation, laxative abuse, diuretic use, dehydration, or the practice of water loading to artificially increase weight [69]. Metabolic alkalosis occurs in patients who vomit or abuse diuretics and acidosis in those misusing laxatives [103]. Hypokalemia frequently results from purging by vomiting or laxative abuse. Hyponatremia is often due to excessive water intake, but may also occur in chronic energy deprivation or diuretic misuse [103]. Symptoms of electrolyte abnormalities are rarely present or are denied by patients [69].

Hematologic abnormalities may include anemia, leukopenia, and thrombocytopenia [105, 106]. These changes are generally attributed to starvation-mediated gelatinous bone marrow transformation, which resolves with proper nutritional rehabilitation [105, 106]. Gastrointestinal abnormalities include slowed gastric emptying, constipation, abdominal bloating and pain, and elevated aminotransferases. Abnormalities of liver enzymes may occur before or during refeeding [103]. Hypercholesterolemia is another common finding but its significance for cardiovascular risk is uncertain [103]. Other abnormalities include micronutrient deficiencies, hyperamylasemia, hypercarotenemia, elevated creatine kinase, xerosis, lanugo-like body hair, acrocyanosis, slower wound healing, and reduced fever response [103, 107–109].

Treatment

Eating disorders are associated with extremely complex medical and psychosocial issues that are best addressed by an interdisciplinary team of medical, nutritional, mental health, and nursing professionals who are skilled and knowledgeable in working with adolescents with eating disorders and their families [57, 110]. Initial evaluation of the adolescent with a suspected eating disorder includes establishment of the diagnosis; determination of severity, including evaluation of medical and

Table 7.7 Indications for hospitalization of an eating disorder

1.	Severe malnutrition (weight <75 % average body weight for age, sex, and height)
2.	Dehydration
3.	Electrolyte imbalance (hypokalemia, hyponatremia, hypophosphatemia)
4.	Cardiac dysrhythmia
5.	Physiological instability
	a. Severe bradycardia (heart rate <50 beats/minute, daytime; <45 beats/minute at night)
	b. Hypotension
	c. Hypothermia
	d. Orthostatic changes in pulse (20 beats per minute) or blood pressure (10 mmHg)
6.	Arrested growth or development
7.	Failure of outpatient treatment
8.	Acute food refusal
9.	Uncontrollable binging and purging
10.	Acute medical complications of malnutrition (e.g., syncope, seizures, cardiac failure, pancreatitis)
11.	Acute psychiatric emergencies (e.g., suicidal ideation, acute psychosis)
12.	Comorbid diagnosis that interferes with the treatment of the eating disorder (e.g., severe depression, obsessive compulsive disorder, severe family dysfunction)

Based on data from [57, 110]

nutritional status; and performance of an initial psychosocial evaluation. Depending on the patient and family circumstances, various levels of treatment options are available for adolescents with eating disorders (inpatient, outpatient, day hospital, or residential treatment). The time to full recovery from an eating disorder may take several years [111].

Indications for hospitalization are listed in Table 7.7 [57, 58, 110]. The main goals of inpatient treatment are medical stabilization and weight restoration through nutritional rehabilitation (about 2–3 lbs per week). Recent studies have shown that safe weight gain can occur starting with approximately 1,400—2,000 kcal/day with regular nutritional advancements [96, 112–114]. Close monitoring of weight, vital signs, fluid shifts, and serum electrolytes during the first week of hospitalization is recommended [96, 112–114]. Attempts should be made to achieve weight gain through the oral route; however, short-term nasogastric feeding may be necessary in some patients. Supplementation with calcium (1,300 mg/day), in accordance with the Institute of Medicine recommendations for adolescents [115] and vitamin D (600–1,000 IU) is often necessary. The recommended length of hospitalization has not been established, although risk of relapse is lower in patients who are discharged closer to ideal body weight compared to patients discharged at very low body weight [116].

All adolescents with eating disorders should undergo a mental health evaluation, and be evaluated for potential treatment, which may include the use of anxiolytic or

antidepressant medications. Although there remains relatively little research on interventions that address the complex mental and physical needs of adolescents with eating disorders, evidence-based research supports that family-based treatment, also known as the Maudsley approach, is an effective first-line outpatient treatment for adolescents with eating disorders and protective against relapse, particularly in anorexia nervosa [117–120]. Family-based treatment is an intensive outpatient treatment that utilizes parents/caregivers as a primary resource to renourish their affected child or adolescent [121]. Typically, one therapist is involved, along with a physician to provide medical care [122]. Although family-based treatment is effective for adolescents with bulimia nervosa, cognitive-behavioral therapy that focuses on changing the specific eating attitudes and behaviors that maintain the eating disorder may be more effective in older adolescents and young adults [123]. The evidence for binge-eating disorders in adolescents is insufficient to draw any conclusions; however, cognitive-behavioral therapy, interpersonal therapy, and dialectical behavior therapy may be helpful [123]. It is important to note that correction of malnutrition is required for the mental health aspects of care to be effective.

The literature regarding treatment efficacy and outcomes for eating disorders in adults is of highly variable quality [120, 124]. Current evidence does not suggest any one particular psychotherapeutic modality for adults with anorexia nervosa [125]. In bulimia nervosa, cognitive-behavioral therapy is frequently used and may reduce the risk of relapse after weight restoration [110, 124, 126, 127]. Psychological interventions that have shown effective in the treatment of bulimia nervosa also show promise in binge-eating disorder, particularly modified cognitive-behavioral therapy, interpersonal therapy, and dialectical behavior therapy (dialectical behavior therapy, also known as DBT, combines cognitive-behavioral approaches for emotion regulation and reality-testing) [128, 129].

The literature on pharmacologic treatment in either in the acute or maintenance phases of anorexia nervosa remains sparse and inconclusive [38, 130]. There is currently no strong evidence of beneficial effects using antidepressants and antipsychotics in adolescents and adults with anorexia nervosa [130, 131]. Medications, specifically selective serotonin reuptake inhibitors (such as fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) may be used to treat comorbid psychiatric disorders such as anxiety, depression, and obsessive compulsive disorder or behavior [132]. There is conflicting evidence as to whether antidepressants reduce the risk of relapse in older adolescents with anorexia nervosa who have attained 85 % of expected body weight [133]. The use of atypical antipsychotics in adolescents with anorexia nervosa is encouraging; however, it is limited to case series and case reports [134–136]. These medications have been shown to be effective in reducing anxiety and obsessional thinking in adolescents with anorexia nervosa.

Antidepressants have been shown to have a positive effect in patients with bulimia nervosa. Fluoxetine is the only medication approved by the FDA for the treatment of bulimia nervosa resulting in decrease in binge-eating and purging episodes in 55–65 % of patients [127]. Antidepressant medication in combination with cognitive-behavioral therapy appears to be superior to either modality alone in the treatment of older adolescents or adults with bulimia nervosa [137].

Prognosis

Eating disorders are marked by a serious course and outcome in many afflicted individuals. In anorexia nervosa, there is an almost 18-fold increase in mortality, including a high suicide rate, chronic course in approximately 20 %, and more than half of patients showing significant psychiatric comorbidity [138]. The prognosis for adolescents with anorexia nervosa is better than for adults, mainly due to the shorter duration of illness and younger age at diagnosis [138–140]. Other factors associated with good prognosis include early identification and treatment, less weight loss, and strong support network [38, 141]. Worse prognosis is associated with a history of extreme or precipitous weight loss, vomiting, and somatic and psychiatric comorbidity [141, 142]. Recovery tends to follow the rule of thirds: one-third of patients fully recover, one-third resort to disordered eating strategies and behaviors as their default coping strategies, and one-third have a chronic and relapsing course [138, 139, 141, 143]. Little research has been done into the prognostic factors and outcome of bulimia nervosa and binge-eating disorder.

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Chapter 8
Stress Fracture

Keith J. Loud

Introduction

Stress fractures are associated with the deleterious components of the female athlete triad spectrum and are a source of significant morbidity among women participating in military readiness training, in addition to those engaged in athletics. Prevention and early identification of the female athlete triad, addressed elsewhere in this textbook, are therefore important strategies to prevent this injury in female adolescents and young adults. This chapter will focus on helping clinicians understand when a diagnosis of stress fracture warrants consideration for further evaluation of the triad.

Definition

Stress fractures are often defined as skeletal defects that result from repetitive application of stresses below the threshold at which a bone would fracture in a single loading [1]. A pathophysiologic model for the injury suggests that bony deformation under increased loading leads to compression of intra-osseous microvasculature, ischemia, and decreased oxygen perfusion, triggering osteoclast-mediated bone resorption [2]. Alternative studies demonstrate propagation of micro-fractures, or "cracks," within bone, which similarly stimulate osteoclasts [3]. In either case, new bone formation by osteoblasts lags bone resorption by 2–3 weeks; if bone-loading activity increases or maintains a high level, the osteoclast activity may

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Table 8.1 Stress fracture grading

	X-ray	MRI	Treatment
Grade 1 "Stress reaction"	Normal	Positive on STIR image only	3 weeks rest
Grade 2 "Stress injury"	Normal	Positive STIR *plus* positive T2	3–6 weeks rest
Grade 3 "Stress fracture"	Discrete periosteal reaction	Positive STIR, *T1* and T2, without definite fracture line	12–16 weeks rest
Grade 4 "Stress fracture"	Periosteal reaction and/or fracture	Positive STIR, T1 and T2 *plus* fracture line	16+ weeks rest

Adapted from [3], with permission from Elsevier

outstrip the reparative ability of the osteoblasts, resulting in a disruption of the integrity of the bony architecture—a fracture. Although the clinical presentation is virtually always pain in the affected bone, the spectrum of injury on radiographic studies can range, depending on the modality and grading scheme, from stress reaction to stress injury, culminating in stress fracture (see Table 8.1) [4].

Epidemiology

Stress fracture is a relatively uncommon injury in the general populace. According to a large cross-sectional survey of adolescents, the lifetime prevalence was below 4 % [5]. Estimates of the burden of injury are, therefore, widely variable when studying smaller groups. Fifteen percent of all reported stress fractures are sustained by distance runners, in whom that diagnosis accounts for half of all injuries [6]. A large study of intercollegiate athletes noted twice the incidence of stress fracture among women compared to men [7]. In studies of military populations, the rate ratio has been reported as high as 10 to 1 [8–12], with up to 20 % of female recruits in basic training sustaining a stress fracture [9–13]. In the broader population of ambulatory adolescents and young adults, no such gender difference has been noted [14]. Otherwise, studies in adult populations have shown increased prevalence with age [8, 11], and Caucasian or Asian ethnicity [11].

Risk Factors

Prevention of stress fracture, as with any injury, starts with identification of risk factors. Low injury rates make definitive determination of risks challenging. Many authorities categorize factors as either intrinsic to the athlete or related to external

exposures (extrinsic). In either category, only some elements are modifiable. In addition, a study of nearly 900 United States Military Academy (USMA) cadets developed a multivariable model in which the maximum variance in risk of stress fracture explained by all potential predictors was only 10 % [9].

Extrinsic Factors

Among the putative causes for stress fracture are factors related to the bone-loading activities, including training surface, techniques, equipment including footwear, and coaching. By far the greatest factor is training volume, which incorporates intensity and quantity, the latter of which is more easily studied. In the Growing Up Today Study (GUTS), a cross-sectional survey of 5,461 daughters of the nurses participating in the national Nurses' Health Study II, engaging in greater than 16 h/week of moderate-to-vigorous physical activity conferred a 79 % increased odds of reporting a history of stress fracture. Every hour of high impact physical activity was associated with an odds ratio (OR) for stress fracture of 1.05 (95 % confidence interval, CI: 1.02–1.09), with running (OR 1.12, 95 % CI: 1.05–1.21) and cheerleading/gymnastics (OR 1.12, 95 % CI: 1.03–1.21) the most significant culprits [5]. A subsequent prospective study of a similarly derived cohort of 6,831 girls refined the findings, with both 12–16 h/week of such activity (hazard ratio, HR 2.78, 95 % CI: 1.41–5.47) and 16–20 h/week (HR 2.65, 95 % CI: 1.37–5.12) associated with even greater risk of stress fracture(s). Running and cheerleading/gymnastics showed the same 12 % increased risk of injury for every hour of participation, as did basketball, in this sample, with hours of any high impact activity associated with an HR of 1.08 (95 %CI: 1.05–1.12) [15].

Intrinsic Factors

Biomechanical factors such as lower extremity alignment, including the so-called Q-angle formed at the knee by the axes of the femoral and tibial shafts; hip, knee, and ankle flexibility; mid-foot hyper-pronation; constitutional hypermobility; and core and lower extremity strength have all been examined for potential associations with stress fracture, without consistent findings. Calf girth measurements have shown promise related to tibial stress fractures, probably due to the protective effect the calf muscles can provide the tibia in absorbing repetitive ground reactive forces in running [16].

The interplay between muscle and bone is also demonstrated by the few studies that attempt to quantify overall physical fitness. In male USMA cadets, those who exercised <7 h/week in the year prior to entry had twice the risk of sustaining a stress fracture than those who trained more [9]. Among women recruits entering the

Army, those who failed a pilot 5-min step test for fitness at pre-entry examination had a 76 % increased incidence of stress fracture during training [17]. Examination of female US Marine Corps recruits identified low aerobic fitness and <7 months of pre-boot camp lower-extremity weight training as risk factors for stress fracture in logistic regression modeling [18], while in a large cohort of 2,345 Finnish women military personnel, poor muscle strength and a poor result in a 12 min run were associated with bone stress injuries [8]. An interesting finding associated the subjective report of "burnout" with stress fracture in female Israeli military recruits in basic training [19]. A systematic review of stress fractures in both athletic and military populations speculated that overall physical fitness is more important to injury risk than other factors, with the observed increased prevalence in women possibly attributable to poorer pre-activity fitness, which has typically not been measured, either in studies or routine pre-participation evaluations [10].

In a case-control study of female adolescents presenting to a sports medicine clinic with stress fractures prospectively diagnosed by radiographs, reported family history of osteoporosis or osteopenia was the only significant predictor, with an OR of 2.96 (95 % CI: 1.36–6.45), controlling for all other important potential risk factors [20]. The prospective GUTS mentioned above [15] confirmed this finding, as did a large cross-sectional analysis of 2,312 active duty army women, which also identified white race as a risk factor for stress fracture [21]. Most other studies have not examined this covariate. Few small studies have examined polymorphisms in the estrogen receptor, androgen receptor, lactase [22], and vitamin D receptor (VDR) genes, with only polymorphisms in VDR significantly associated with stress fracture in male military personnel [23].

Bone Resilience

Most research attention has been paid to the intrinsic ability of the skeleton to withstand the repeated stresses that cause injury. Examinations of bone geometry have demonstrated an expansion of cross-sectional area and cortical thickness related to the ground reactive forces of running and jumping, but thresholds have not been established that correlate with stress fracture [24]. Increased use and standardization of advanced imaging techniques like peripheral quantitative computed tomography (pQCT) may allow for better understanding of the geometric and architectural parameters that can resist stress fracture.

Our greatest understanding of bone quality, therefore, comes from investigations of bone mineral density (BMD). Starting with Myburgh's sentinel 1990 matched case-control study of 38 adult female runners, there has been a growing body of consistent evidence that at least some stress fractures are associated with decreased BMD [25]. This literature includes retrospective [26] and prospective studies of American [27–29] and international [16] track and field athletes as well as American [21] and Israeli [19] female soldiers. The association between low BMD and stress fracture persists in meta-analyses [30].

Menstrual Function

Menstrual history has been a less consistent predictor of stress fracture in studies examining this factor. The GUTS cohort studied in 2005 demonstrated that being post-menarcheal was protective against stress fracture, with an OR 0.61 (95 % CI: 0.40–0.93) in an adjusted multivariable model [5]. The subsequent prospective GUTS estimated at least a 30 % increased risk (HR) of stress fracture for every year later age of menarche [15]. In addition to family history of stress fracture, Friedl's large military study identified history of amenorrhea as a risk factor for stress fracture [21]. A prospective analysis of female USMA cadets demonstrated a 44 % decrease in stress fracture risk for every additional year since menarche [9]. The association with delayed menarche was first noted by Warren et al. in ballet dancers in 1986 [31]. In addition to delayed menarche [16, 26] conferring increased risk, most [16, 18, 21, 25, 28, 32, 33], but not all [20, 27, 29] cohort and case-control studies have found an association between a variety of measures of current menstrual function and stress fracture.

Nutrition

Although the association of athletic energy availability with risk of stress fracture has not been studied, general nutritional status is associated with injury, with active females who are underweight (e.g., <75 % ideal [34]) having increased rates [11]. In women soldiers, lowest adult weight is associated with risk of stress fracture (although not current weight) [35]. In the prospective matched case-control study performed in Boston, increased BMI was associated with odds of stress fracture, perhaps as a proxy for decreased fitness levels, although the effect was mitigated and not significant in multivariable models [20]. Field's large prospective GUTS cohort did not demonstrate any significant association between stress fracture and being either overweight or underweight [15]. Moreover, positive responses to disordered eating behaviors by these girls on the Youth Risk Behavior Surveillance System questionnaire did not show any association with stress fracture [15].

Other studies have associated elevated cognitive dietary restraint ratings (although not frank disordered eating) [26, 36, 37] and increased eating disordered inventory (EDI) scores [38] with impaired BMD in active female adolescents, independent of menstrual history. Few have directly linked elements of disordered eating with stress fracture, perhaps due to the low incidence of this injury in most studied cohorts, although one study did associate self-reported stress fracture with measures of compulsive exercise, controlling for global scores on the Eating Disorder Examination Questionnaire (EDE-Q) [39].

Dietary intake of the primary macro- (dairy) and micro-nutrients (calcium and vitamin D) associated with bone health have not shown consistent associations with stress fracture risk. Myburgh's early study did demonstrate lower dietary calcium and dairy intake in cases with stress fracture, but a review of the literature showed

that most cross-sectional and population-based studies do not support this finding [40, 41]. However, two prospective studies, including a randomized clinical trial (RCT) in female navy recruits [42], demonstrated a protective effect of increased current dietary calcium intake [42, 43]. Among young adult female competitive distance runners, higher intakes of skim milk and other dairy products were also protective [43]. Vitamin D has been less well studied, although the naval RCT also supplemented vitamin D to 800 IU daily over 8 weeks [42]. Among adolescents, a prospective analysis of food frequency questionnaires of the participants in the GUTS cohort demonstrated a protective effect among those in the highest quintile of vitamin D intake (HR 0.48, 95 % CI: 0.22–1.02, $p = 0.04$ for trend), stratifying for at least 1 h of weekly moderate-to-vigorous physical activity [44].

Clinical Applicability

As addressed elsewhere in this text, assessment of nutritional status and menstrual history constitute essential health promotion for female athletes, with attention to correct any identified deficits, especially in those who have sustained a bony injury. The dilemma posed to the clinician managing a patient with stress fracture is therefore whether to evaluate BMD. In 2007 the International Society for Clinical Densitometry developed guidelines to help identify children and adolescents who might warrant skeletal assessment by dual emission X-ray absorptiometry (DXA). These guidelines defined "clinically significant fractures" as

- Any long bone fracture of the lower extremities
- Vertebral compression fractures
- Two or more long bone fractures of the upper extremities

but did not specifically address stress fractures [45].

It is the clinical practice of this author to consider any stress fracture sustained with fewer than 8–12 h of weekly moderate-to-vigorous physical activity as a potential indicator of skeletal fragility, prompting a discussion of the value of DXA screening with the patient and family. Although stress fractures sustained with greater than 12–16 h of weekly moderate-to-vigorous physical activity may represent fatigue failure of structurally normal bone, the following factors should increase one's index of suspicion for skeletal insufficiency:

- Family history in first or second degree relatives of osteoporosis, osteopenia, or low BMD
- Other comorbidities known to decrease BMD
- Any stress fracture of the humerus, radius, or ulna unless the athlete impact loads the upper extremities (as in gymnastics and cheerleading)
- Vertebral compression fractures
- Two or more stress fractures in the lower extremity

– Fractures in bones with a high proportion of cancellous bone [46], such as the

  - Calcaneus
  - Tarsal navicular
  - Talus
  - Femoral neck
  - Pelvic ring and sacrum
  - Pars interarticularis of the vertebral bodies (acquired spondylolysis)

Further work-up of low BMD for age identified by physicians skilled in the interpretation of DXA results in children, adolescents, and young adults should proceed as described elsewhere in this text.

Diagnosis

An important caveat to pursuing further investigation is a high degree of certainty in the diagnosis of bony stress injury. A common radiographic scheme for grading stress injury is presented in Table 8.1. It demonstrates the increased sensitivity of magnetic resonance imaging (MRI) when compared with plain radiographs. Nuclear medicine bone scans are as, if not more, sensitive than MRI, but lack specificity and anatomic localization. Computed tomography (CT) is sometimes used to further characterize the anatomic detail of stress fractures at risk for nonunion, but the radiation exposure should limit routine use.

Most of the clinical investigations associating stress fracture with low BMD used radiographic evidence of fracture as the outcome of interest. The larger epidemiological surveys relied on self-reported history of stress fracture, which may not have been confirmed radiographically. It is therefore possible that any injury along stress continuum could indicate bony insufficiency, but unless further evidence addresses this question, it is not indicated to obtain expensive advanced imaging (MR, CT, bone scan) for all stress fractures. Plain radiographs at least one month from the onset of symptoms should demonstrate periosteal reaction and callus formation, should confirmation be desired.

Management

Healing time for common stress fractures is outlined in Table 8.1. Treatment is focused on removing the active person from activities that aggravate symptoms, which sometimes necessitates crutches, bracing, or other assistive devices until activities of daily living can be completed without any pain. Physical therapy can address any deficits in strength or flexibility identified on examination, and prescribe exercises to maintain general fitness and conditioning. Lappe's finding that a

longer history of regular exercise was protective against stress fracture in military recruits reminds us of the benefits of physical activity [35]. Therefore the goal should be "relative rest," with swimming and other non-load bearing exercises substituted for the offending activity. Some authorities return patients to 50 % of their pre-injury training volume when they are asymptomatic in activities of daily living without assistive devices. Increases of no more than 10 % in total training volume each week are allowed as long as they remain completely pain free. Other than addressing identified deficiencies, supplementing dietary calcium and vitamin D does not speed healing of fracture.

Referral

Stress fractures that have a significant rate of nonunion or are rarely encountered should be referred to clinicians with expertise in their management, such as orthopaedic surgeons or sports medicine specialists. These include the pars interarticularis (spondylolysis), pelvic ring and sacrum, femoral neck, anterior tibial cortex, medial malleolus, tarsal navicular, talus, patella, great toe sesamoid, 5th metatarsal, and 2nd metatarsal base [1].

Prevention

Given the correlation with low BMD, prevention of stress fracture equates to promoting good bone health, including good general nutrition with attention to adequate energy availability and adequate consumption of sources of vitamin D and calcium, avoidance of tobacco and excessive alcohol [21], and recognition and early identification of the female athlete triad. Exercise should be promoted, limiting moderate-to-vigorous physical activity, particularly high impact loading activities, to no more than 12–16 h weekly.

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Chapter 9
Female Athlete Triad: Rehabilitation and Psychological Implications

Richard D. Ginsburg and Lenore Herget

Introduction to the Triad

Participation in sport is linked to numerous physical and psychosocial benefits. It can improve motor skills, peer relationships, cognitive function, and overall health and well-being [1]. In contrast, there are concerns for athlete's overall health, as the demands of sport specialization and rigorous training regimens rise. Physical strain on athlete's musculoskeletal system and emotional state are linked to an unsafe decline in health. When combined with poor health habits, this level of demanding and overzealous training places athletes at risk for significant medical setbacks.

The Female Athlete Triad, a continuum of illness involving some combination of disordered eating, oligomenorrhea/amenorrhea, and decreased bone mineral density with inherent risk for osteoporosis, is among the dangerous diagnoses that female athletes encounter [2]. With accurate diagnosis and treatment, the Triad can be prevented. Without accurate and timely diagnosis, irreversible physical and psychological damage occurs, affecting every aspect of the athlete's life. Often, higher level cognitive functioning and concentration suffer, mood changes and withdrawal behaviors begin to surface, and muscle weakness from malnutrition and dehydration lead to insufficient energy stores, ultimately increasing the risk for cardiovascular and other system involvement [3].

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Early identification of the Triad is difficult to establish as the signs and symptoms exhibited with the diagnosis can look like an athlete simply working harder to become better at her sport. Aside from being involved with the athlete's care once she is injured, physical therapists are commonly the clinicians who are most involved with all aspects of the athlete's care [4]. From speaking with the athlete and her parents to the involved physician, the physical therapist is often the first line of defense when identifying at-risk athletes. Coaches also play a role in the identification and recovery of these athletes. Coaches have access to medical, educational and personal information on each of their athletes, giving them an advantage in overall recognition of atypical behavior. Armed with the knowledge of at-risk behaviors, a coach can be the first line of defense in the development of or progression of the Triad. When these behaviors become apparent, the coach can consult the medical team to get the athlete evaluated. With a relationship based on trust and compliance, most athletes will listen to recommendations from their coach.

Implication of Disordered Eating

The Triad begins with a lack of deficiency in energy or calories to support the amount of stress being applied to the body. The lack of fuel or energy for the body results in loss of strength, impaired breathing and heart function and difficulty concentrating; none of which contribute to peak performance. Athletes who participate in aesthetic sports, whose sport requires minimal clothing, including ballet and gymnastics, along with endurance running and cycling athletes, are often under the perception that carrying less weight will improve performance. Incidentally, caloric intake affects athletic performance by providing appropriate muscle glycogen stores. Deficiencies can lead to hypoglycemia and electrolyte abnormalities. If not addressed, the athlete may become chronically undernourished.

When an athlete loses weight through moderate to severe diet restriction, she is at risk for reduced bone density, and specifically, alterations in bone resorption and formation [5]. These restrictive habits can also lead to decreased body weight which predisposes athletes to oligomenorrhea, infrequent or very light menses, and in more severe cases, amenorrhea [3]. Low levels of estrogen associated with amenorrhea have a negative effect on muscle function [6] and may result in progressively more porous bones, leading to eventual risk of fractures. Providing these athletes with the knowledge of their need to increase caloric intake to fuel the physical demands placed on their body is necessary to prevent or minimize sequelae of the Triad.

The physical therapist often is the first to observe an athlete's disordered eating and exercise behaviors [4]. Knowing which questions to ask during an evaluation can help guide decision making and referral process. Pre-participation exams, conducted by referring physicians or the physical therapist, offer a forum to ask these screening questions. The questions should address all components of the Triad, including disordered eating, body image, menstrual history, and bone health.

Specific questions pertaining to the athlete's training regimen can highlight problems.

List 9.1: Training
- Do you have pain with weight-bearing?
- Does your weekly running mileage exceed 40 miles per week?
- Is the pain worse with running and jumping?
- What do your typical daily workouts look like?

Daily rigorous exercise *in addition* to regular training sessions required by the sport can be a warning sign. Questions pertaining to the athlete's general nutrition should follow.

List 9.2: Nutrition
- What are your typical daily eating habits?
- What is your rough caloric intake?
- Are you happy with your current weight?
- Have you had any fluctuations in weight: weight loss, weight gain?

Most females will often hide or deny their disordered eating behaviors [1] so gently asking these questions can be a useful tool not only in the identification of a problem, but in raising the athlete's self-awareness. Rapid fluctuations in weight, particularly weight loss, in addition to excessive leanness, can be a warning sign of disordered eating. Additionally, a history of wide fluctuations in weight over short periods of time is indicative of an athlete's preoccupation with weight, food, and diet. If necessary, consults with nutritionists can be arranged to assist with disordered eating.

Nutrition and Its Effect on Bone Mineral Density

As part of their evaluations, nutritionists may identify nutritional deficiencies and recommend supplements for calcium and vitamin D. Nutritionists are wise to give special attention to younger athletes who are particularly vulnerable to these nutritional deficiencies. From infancy to adolescence, when bone growth is at its peak [7], young females greatly depend on high levels of calcium intake for healthy bone growth. Appropriate calcium intake is also critical during this period because urinary calcium excretion increases until the end of puberty [3, 8]. Unfortunately, calcium intake among females typically declines during adolescence when bone calcium requirements are at their highest and maximum bone growth is occurring [3]. Due to the potential discrepancies between what young female athletes need in terms of nutrition and what they actually consume, a nutritional evaluation can be an essential preventative intervention.

The nutritionist can also provide dietary guidelines to help regulate the athlete's weight. Weight gain can lead to a more predictable, consistent menstrual cycle which increases estrogen production. This may ultimately lead to an improvement in bone density. In the case of already damaged bone, bone stimulators may be provided, for possible assistance in bone remodeling and healing. Though high quality evidence does not exist for the efficacy of bone stimulators for healing fractures, there are some mixed data that suggest an increase in healing activity may occur with the use of stimulators on slow-to-heal fractures [9]. Additional research is required to draw conclusions and make definitive recommendations of its use.

Implication of Amenorrhea and Abnormal Menses

The induced energy mismatch and subsequent depletion from vigorous exercise participation and inadequate nutritional intake results in the relative "shut down" of the reproductive system by the hypothalamus [10]. Because of this, amenorrhea tends to be higher in the athletic population. An athlete with amenorrhea can lose up to 5 % of her bone mass per year, ultimately increasing her risk for stress fractures [3, 11, 12]. Stress fractures can sideline an athlete from her sport for a prolonged period of time as the fracture can be slow to repair when the athlete is undernourished. Questioning the athlete about her menses can help with determination of her stress fracture risk as it is shown that females who miss more than half of their menses have significantly decreased vertebral bone mass when compared to normative values [3].

Clinicians may inquire about menstruation by asking the following questions:

List 9.3: Menstruation
- What was the age of your first menses?
- Have there been any changes in your menstruation?
- Do you have monthly menstrual cycles?
- How long do your cycles last?

The age at which a female first menstruates is correlated with bone health [13]. Females who are diagnosed with disordered eating, specifically anorexia nervosa, before their first menstruation have a lower bone density than those who develop the disorder later in life [13]. Many athletes and coaches believe that irregular menses is simply part of the training effect when participating in competitive level sport. It is evident, though, that the bone loss that occurs with disordered menses is not part of the training effect. Most bone mass, roughly 90 %, is reached by the end of adolescence [12]. Peak adult bone mass is reached by the third decade of life and is a major predictor of fracture risk for the female athlete [3]. It is suggested that continuous exposure to endogenous estrogen during menses has been linked to greater adult bone mass, as estrogen is necessary for maintaining calcium content in the bone [3].

Hammond et al. looked at the effects of impact loading exercises, nutritional intervention and supplements aimed at bone metabolism or remodeling and found that high impact jumping and nutritional assistance is insufficient to prevent bone loss in endurance athletes. Despite the increase in bone mass that is found with weight-bearing exercise, the consistent underexposure to estrogen surpasses any possible benefits. Complicating matters are the endurance cyclist athletes; who, according to longitudinal studies, lose bone mass over the course of their training season [14]. Further research is needed when considering prevention and treatment strategies for this athletic population.

Implications of Low Bone Density

In addition to being affected by abnormal menses, females may be at an increased risk for injury due to their muscle to fat ratio [11]. Females have lean body mass, less strength, power, and speed compared to their male counterparts. They typically experience their growth spurt earlier in life than males, leading to more stress and strain on the bones before the muscles have a chance to develop as bone growth supersedes muscle fiber recruitment and growth [12]. Along with the structural orientation differences, this added stress and strain can predispose females to more alignment associated injuries. A complete musculoskeletal physical examination is necessary.

Physical Therapy and Its Role in Managing Triad Related Injuries

A physical therapist can play a critical role in the assessment and treatment of bone-related injuries. After a referral from the prescribing physician or the patient's primary care physician, the physical therapist, well trained in sport performance, can conduct an initial evaluation that include a full musculoskeletal assessment of joint mobility and range of motion, muscle length and flexibility, muscle stability, strength and endurance, and functional performance of sport-specific tasks. Results provide valuable information from a potential risk for injury standpoint to preventative training tips [15]. As necessary, physical therapy sessions may occur weekly, biweekly, or monthly to address impairments in any of the above areas. Less frequent, summative re-evaluations may be scheduled with the prescribing physician to assess overall improvement.

In addition to the general system screen, flexibility, joint motion and strength assessment, the performance evaluation may also include more specific functional tests, such as the Single Leg Hop Test and the Percussion/Vibration Test, which are sensitive to screening for skeletal abnormalities [12]. The athlete may exhibit an increase in pain with the single leg hop test as this test requires the athlete to land on her heel. Landing on the heel does not allow for any talocrural joint motion to assist

with shock absorption of the ground reaction forces. Bony involvement and or joint dysfunction may be present. An increase in symptoms with vibratory testing may be suggestive of a stress fracture as the vibratory instrument is placed directly over the painful region. Bone injuries are more sensitive to vibration [12].

Additional contributing information gathered at the initial visit, either with the physical therapist or referring physician may include imaging. MRI has the highest sensitivity in detecting stress fractures [16]. Bone density testing, bone scans, and radiographs may also be utilized [16].

List 9.4: Associated Laboratory Metrics and Symptoms [17]

- Hematology
- Biochemistry (electrolytes, iron, calcium, total protein)
- Hormonal profile (TSH, T3, T4, cortisol)
- Complaints of light-headedness, dizziness, headaches, or fatigue without respiratory or vestibular dysfunction
- Complaints of weakness or increase in muscle cramping

Many female athletes sustaining an injury have weak surrounding muscles and decreased bone mineral density. Physical therapists who possess extensive training and experience with the female athlete's anatomy, specific sport, and the most commonly associated injuries female athlete's encounter are best equipped to guide the athlete's plan of care and pave the road to recovery. This can be especially true when working with an athlete diagnosed with a stress fracture. Females are at increased risk (1.5–5.0 times) for developing a stress fracture when compared with their male counterparts. Twenty percent of female runners will develop a stress fracture at some point in their life due to the repetitive microtrauma that running involves [18]. The combination of extrinsic risk factors such as training errors and insufficient rest time between runs, and intrinsic biomechanical and biochemical risk factors can be a precursor to the development of stress fractures. If the bones are not given adequate time to remodel after the microtrauma that running induces, the athlete is predisposed to asymmetrical loads due to her faulty biomechanics placing her at further risk. Additionally, adolescent females whose growth plates have not closed and are still building bone may not build enough bone if they are undernourished, thus increasing their future risk for fractures [19].

Steps can be taken to minimize risk of stress fractures. Emphasizing the importance of cross training for multidirectional loading and addressing biomechanical dysfunction including muscle weakness and imbalance, joint hypomobility, muscle inflexibility, and dynamic control of faulty anatomic alignment can improve symptoms and ultimately sport performance. Many female athletes, who participate in uni-directional sports, like running and cycling, are at more risk for the development of hip stress fractures, as they are mainly performing in the sagittal plane. Because of this, they develop a muscular imbalance between the anterolateral hip and leg

musculature and the posterolateral hip musculature, specifically the gluteus medius. Due to the muscle's attachments to the posterolateral femoral neck facets, improvement in gluteus medius strength can neutralize stress through the femoral neck (a common site for stress fractures in female athletes). The gluteus medius and minimus provide a depressive and compressive force to keep the femoral head centralized in the joint, thus minimizing hip joint damage [20]. If these gluteal muscles are weak, the forces transmitted to the femoral neck increase and can ultimately lead to stress fracture. Improving and maintaining gluteus medius strength and endurance may be a modifiable risk factor for femoral neck stress fractures [19, 20]. In fact, increasing gluteus medius performance can minimize and even prevent other lower extremity overuse injuries that are common to female athletes.

Other modifiable risk factors include the implementation of appropriate training protocols per sport requirements, use of the most compliant training surfaces available and the use of the most appropriate footwear for the sport. This is especially true for runners who are vulnerable to over training. With these running athletes, it is prudent to encourage at least 3 months of relative rest from running per year and set training parameters of an increase in running mileage or time of 10 % per week [21]. Most of the literature indicates that the running athlete has the highest likelihood of developing bone-related injuries, given the repetitive nature and pounding of the sport. Other evidence based prevention tips can be found at www.stopsportsinjuries.org [7].

In addition to stress fractures, some other common injuries sidelining females include Anterior Cruciate Ligament (ACL) insufficiency, Osteitis Pubis, and Sacroiliac Joint Dysfunction. The Miserable Malalignment Syndrome was first discussed by *Stanley James* in 1979. He examined the static alignment of females with their wider pelvis, femoral anteversion, genu valgum (i.e., "knock-knee"), external tibial rotation, foot pronation, and lower center of gravity. Based on these factors, in combination with general flexibility, ligament laxity with higher body fat and less cross-sectional muscle, James proposed an increased risk for ACL injury in female athletes [18].

Adolescent females between the ages of 12 and 16 are at an even higher risk for ACL rupture [22]. Comparable to Stanley's Miserable Malalignment, anatomic factors include the fragile combination of knee valgus, femoral notch width and shape and lack of foot pronation control during dynamic activities. Orthopedic factors include the accrual of 90 % of bone mass by age 18 [18]. Coupling these factors with a hormonal surge during the follicular stage of menstruation when estrogen is at its highest, the female adolescent athlete may be at more risk for ACL injury as it is thought that estrogen may reduce collagen synthesis and contribute to ligament laxity and muscle weakness [23].

Because of this gender related risk, ACL prevention programs have been established to combat the muscle imbalances and anatomical alignment that these young females possess [6]. Including a nutrition consult and a sports performance-specific education component in these prevention programs help to identify and manage females who are at increased risk for developing any components of the female

athlete triad diagnosis, as this age is a prime target for environmental and social influences on the female body. Many hospital based and well-established private sports medicine clinics have either developed ACL prevention programs or provide links to existing programs, such as "Sportsmetric's 'Warm up for Injury Prevention and Performance' or 'WIPP'" and "Santa Monica Sports Medicine Foundation's 'Prevent Injury and Enhance Performance'" or "PEP." Both programs involve a comprehensive warm-up program, developed by physicians, physical therapists, athletic trainers, and coaches that address muscle imbalance, strength and flexibility asymmetry, stability and coordination through sport-specific movements [24]. Although, somewhat lacking in the quality of evidence, they are the two most cited programs in the literature and have been validated to decrease the incidence in ACL injury in certain athletic populations [24]. By incorporating all facets of movement patterns, it not only improves dynamic stability but emphasizes correct performance for best motor learning potential. Additionally, it provides alternative exercises to further enhance the program as well as resources for the younger athlete. More information is accessible at http://sportsmetrics.org/ and http://smsmf.org/smsf-programs/pep-program. Physical therapists and other clinicians can reduce the risk of worsening injuries by educating the athlete about her relative risk of re-injury and recommending appropriate training and exercise programs that address muscle imbalance and orthotics as necessary to address anatomical misalignment [18, 25]. If neither the team nor the physician involved provide training parameters or exercise routines for the athletes, valuable resources exist that can be referenced, including Sports Section of the American Physical Therapy Association (APTA), National Athletic Trainer's Association (NATA), and American College of Sports Medicine (ACSM). Along with other evidence based resources, these provide protocols which can be easily referenced on-line.

As indicated, clinical evaluations by sports medicine trained PTs are valuable screening tools to tease out triad risk factors [26]. Furthermore, annual physical exams by the physician are beneficial, as they provide a perfect opportunity to set up psychological counseling for sport participation and performance. Recognizing that cognitive and emotional factors can affect performance and participation can be beneficial when taking a multidisciplinary approach to the athlete's care. Focusing on these factors supports physical and psychological healing, assists the athlete in a healthy return to her previous level of activity and ultimately improves her athletic performance.

Recognition of the power and influence that coaches have on their athletes is a critical component of the recovery process [11]. On the negative side, coaches can contribute to overly intense training regimens and psychological stress that affect the body. On the positive side, coaches can teach valuable coping skills necessary to strong athletic performance and physical endurance. Particularly when athletes face a difficult coach within a demanding and intense sport environment, the sport psychologist can offer support and additional strategies to regain physical and emotional equilibrium.

Psychology of Injury: The Importance of the Psychologist

Over the past decade, the sports medicine field has given greater attention to psychosocial factors affecting injured athletes [27, 28]. Consequently the role of sport and clinical psychologist are growing in importance, particularly in addressing prevention of injury, the recovery process, and treatment compliance [29]. In a recent survey of athletic trainers, anxiety, stress, anger, and treatment compliance are rated as the most central responses an athlete experiences post injury [30]. Underlying these responses are strong emotions such as fear of re-injury, worry about returning to pre-injury baseline performance expectations, sense of isolation, loss of athletic identity, disconnection from adequate social supports, increased pressure to return to play prior to full recovery, and fear of losing one's competitive edge [31, 32].

Among younger athletes, pressure to perform from parents, coaches, and peers can be overwhelming and can lead to performance anxiety and psychological stress for the young athlete [33, 34]. The highly touted 10,000 h rule first described in Ericcson's study of elite musicians and then highly popularized in Malcolm Gladwell's *Outliers* [35] sends a powerful message to young athletes, their families, and coaches that early and extreme training is the path to athletic excellence [36]. As a result of this culturally prominent belief, many young athletes play year-round sports and or play more than one sport in a season from a young age. In addition to the risk of injury and stress, athletes are vulnerable to burnout and diminished enjoyment [37]. Psychologists and other treatment providers must attend to the developmental needs of younger athletes as they provide support in the recovery process. In particular, attention to a young athlete's need for support vs. an older athlete's drive for achievement and independence can influence how treatment providers offer care [33, 38].

Psychologist's Role in the Management of the Triad Athlete

The most effective management of injured athletes, and most specifically, the triad athlete, is a multidisciplinary approach that aims at assessing and dealing with all aspects of the problem. Not only does this involve clinicians who can address physical, cognitive, behavioral, emotional, and nutritional aspects of the triad, but it also provides the athlete with options when she needs someone to go to with questions. Athletic injuries can displace an athlete from her social comfort zone and leave her feeling dejected and alone. She may deteriorate physically and psychologically leading to a decrease in her performance. As the athlete often identifies herself by her performance or sport, this decline is likely to exacerbate and perpetuate the downward spiral. Referrals to psychologists who specialize in sport performance and post injury can be beneficial. The importance of the clinician having experience with and an appreciation for sport and the importance of sport in the athlete's life are crucial. The timing of the referral is equally important, as early identification and treatment may prevent the athlete from irreversible damage.

It is also critical for treatment providers to recognize that injuries can be potentially traumatic for athletes. Many athletes may be experiencing their first significant injury in their lives. With minor injuries, athletes feel irritated and inconvenienced. In cases of more serious injuries, the greater the risk for psychological difficulties. Often injured athletes feel a loss of stability and control. They can withdraw from others in an attempt to protect themselves, or they may become hypervigilant in their recovery, placing them at greater risk for further injury and delay of healing. It is critical that the entire treatment team (physician, nurse, physical therapist, and psychologist) understands the need for reassurance, an explanation of how the injury occurred and how it will heal, a defined treatment plan, and ongoing connection with caring and supportive friends, family, and treatment providers. Treatment providers can create a supportive structure that centers the injured athlete, restores a sense of safety, and increases a sense of hope for full recovery [39].

Each injured athlete is unique. There is no one approach that works for all. A treating psychologist receiving a referral for an injured athlete must assess various psychosocial factors prior to implementation of any intervention. Initially, key questions require consideration.

List 9.5: Pre-screening Psychosocial Questions

- Does the athlete suffer from an underlying depression or anxiety?
- Are their outside factors such as family pressures, relationship dynamics, coach or teammate conflicts affecting the athlete's self-esteem?
- Are there cognitive distortions about the importance of training and performance that require examination?

Such questions, while critical, need to be raised tactfully and sensitively. Competitive athletes can be highly defended and prideful. Frequently, they prefer to feel invulnerable and are unwilling to examine their weaknesses or flaws. Dialogue with patients needs to focus on their strengths and pathways to recovery with explicit rehabilitative steps and goals. Feeling a sense of accomplishment, even if minor, is therapeutic to athletes recovering from injury as it gives them momentum and confidence and reduces the risk of discouragement.

Working with chronic pain patients presents significant challenges for clinicians. When there is no obviously organic etiology for somatic complaints, it is wise to seek a psychiatric consult. While these patients may be experiencing real physical pain, psychological issues may be causing and or exacerbating them. Some patients may have an underlying, characterological pathology such as a personality disorder. These patients are among the toughest to treat and require intensive therapy with firmly defined goals and boundaries. Success for these patients is difficult, even for the most trained therapist. In other cases, there may be an undiagnosed depression or anxiety that is being expressed somatically. In these cases, a combination of therapy and medication can be effective. A consult with a psychiatrist who is savvy with therapy and meds is often an effective intervention.

Treating Disordered Eating

Disordered eating in female athletes is particularly difficult to assess and treat. Athletes are secretive about their food restriction or their binging and purging behaviors. Tremendous shame is accompanied by eating problems and body image issues. Bulimia is the most difficult to assess because athletes appear to be of normal body weight and are highly secretive about their eating behaviors. Attention to more subtle physical symptoms such as cuts on the back of knuckles and halitosis from self-induced vomiting, discolored teeth enamel and multiple cavities, soft baby hair on the skin or male pattern hair distribution, acne, and yellowing of skin are some of the common indicators of an underlying eating disorder [17].

Psychological treatments for eating disordered athletes require appropriate attention to eating behavior and weight while emphasizing the importance of building strength and nurturing oneself. Because disordered eaters often have a distorted sense of their body, it can be counterproductive and even harmful to focus exclusively on their weight and body image. It is also important to focus on how the athlete is feeling about herself and help her to identify a variety of characteristics that are worthwhile and substantial such as her intellect, relationship with friends, sense of humor, and importance to her team among other qualities. Once this greater self-awareness is established, psychologists and other treatment providers are better able to have less charged discussions about weight.

During the assessment and treatment process, it is critical for the psychologist to communicate with the athlete's physician, nutritionist, and physical therapist as each member serves an important role in covering the various components of recovery and relapse prevention. Periodic visits with the physician to assess weight changes in the more serious cases may be necessary. Ongoing dietary guidance is critical as well. While there may be danger to overemphasizing the role of food and eating, there is a greater risk of ignoring or deemphasizing it. Treatment providers need to communicate with each other about the athlete so they maintain appropriate balance between the physical and psychological manifestations of an eating disordered athlete.

Attention must be paid to appropriate levels of physical activity, nutritional intake, and the athlete's ability to cope with the psychosocial challenges that come with sport participation. Many female athletes do not realize that they are at risk for the Triad. If they are physically active, the competitive nature that drives good athletes can be enough to lead to the disorder. Highly competitive athletes are more at risk due to demanding training schedules and the intrinsic and extrinsic pressure to perform well.

Treatment Techniques for Injured Athletes

Psychologists incorporate various strategies to address injury prevention and treatment. Cognitive behavioral treatments focused on stress management reduce the number of days of being injured [40]. Other psychologists utilize the use of imagery

in the rehabilitation process [41]. In addition, in order to increase compliance with recovery regimens, treatment providers experience success establishing short-term goals for their injured athletes [42].

Most psychologists working with an injured athlete will integrate a supportive approach to recovery with cognitive behavioral treatment. For example, an athlete who has an ACL tear and requires surgery may begin to believe that she will never walk again or never play her sport again. Helping athletes recognize that such responses, while understandable, are often distorted, can reduce anxiety and increase hopefulness. Replacing distorted thoughts such as "I will never get better" with "I have a significant injury, but I have great medical care, and I will recover in time" can be a powerful intervention. Similarly, any pain or perceived setback in the recovery process is typical and should be normalized by the treatment team. For example, an athlete may say, "My knee feels more painful today after physical therapist than last time. I must be getting worse." The treatment provider can be reassuring and stabilizing when saying, "It is very common for you to experience soreness after rehabbing. In fact, this is what we expect in the recovery process." Finding ways to interrupt the progressive negative thinking that emerges in the injury recovery process can speed up recovery and reduce risk of further psychological stress or depression.

Should an athlete become so discouraged or isolated as a result of prolonged or difficult recovery, a referral to a psychiatrist for medical consultation may be warranted. A short treatment of a serotonin-reuptake inhibitor (antidepressant) may help avoid over-thinking, anxiety, and diminished mood. Once an athlete recovers and has stabilized her mood, discontinuation of the medication may well be warranted under the supervision of the prescribing psychiatrist.

Conclusion

The multidisciplinary approach to evaluating, treating, and counseling the athlete diagnosed with the Triad and the athlete at risk for developing the Triad is the most beneficial and effective method when working with this population. Recognizing the intense emotional and psychological pressures that are involved at all levels of female athletics, regulating nutritional intake and training regimens, emphasizing the importance and benefits of cross training and addressing innate biomechanical faults or asymmetries with appropriate strength and stability exercises are vital to decrease the likelihood of developing the female athlete triad. Timely communication between the coach and medical team about any atypical behavior of the athlete, as mentioned previously will expedite the identification and management process and likely disable the progression of the Triad. Above all, devoting time and energy toward the prevention of females developing the triad, by educating females from a young age, is the best medicine clinicians can provide.

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Chapter 10
Strategies to Promote Bone Health in Female Athletes

Catherine Logan, Emily Curry, and Elizabeth Matzkin

Abbreviations

ACSM	American College of Sports Medicine
ADA	American Dietetic Association
AED	Academy for Eating Disorders
ANAD	National Association of Anorexia Nervosa and Associated Disorders
BMD	Bone mineral density
DXA	Dual X-ray absorptiometry
IOC	International Olympic Committee
NCAA	National Collegiate Athletic Association
PPE	Pre-participation evaluation

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Introduction

After Title IX Educational Amendment Act passed in 1972, female sport participation skyrocketed from 7 to 41 % in 2009 (Fig. 10.1) [1]. In 1992, 20 years following the enactment of Title IX, the Female Athlete Triad was first defined as an interrelated disorder involving an eating disorder diagnosis, irregular menstruation, and decreased bone mineral density (BMD). The disorder was thought to most commonly affect women participating in weight-dependent sports, such as gymnastics, ice-skating, and endurance running. As many as 50–70 % of female athletes in certain sports will have at least one of the three components [2–11].

However, many athletes remained undiagnosed according to the 1992 definition of the Triad because they did not meet the classic Triad criteria. For example, many young female athletes did not fit the classic "eating disorder" definition but had amenorrhea. By the time they were diagnosed with a stress fracture, treatment options for the Triad became more limited because females can only accrue BMD up until 20–25 years of age. After this time frame, athletes can only try to maintain BMD.

In 2007, the definition transitioned into a spectrum disorder of low energy availability, irregular menstruation, and decreased BMD. The updated definition can also be described as an athlete falling under the "umbrella" of the spectrum of the Triad so that not all three components need to be present for the athlete to suffer from some of the long-term, negative consequences (Fig. 10.2). For example, an athlete may present with only one component of the Triad, such as low energy availability, which makes early interventions possible to prevent progression to the second (irregular menstruation) and third (decreased BMD) components of the Triad.

The true Triad prevalence is unknown for a variety of reasons, including patient population heterogeneity, lack of prospective studies, and lack of studies evaluating all three components of the Triad under the new definition formulated in 2007. The

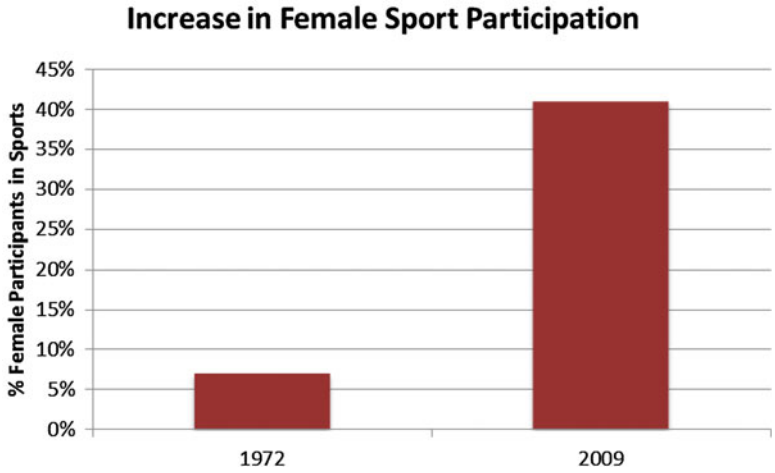

Fig. 10.1 Female sport participation increased from 7 % in 1972 to 41 % in 2009 as a result of Title IX

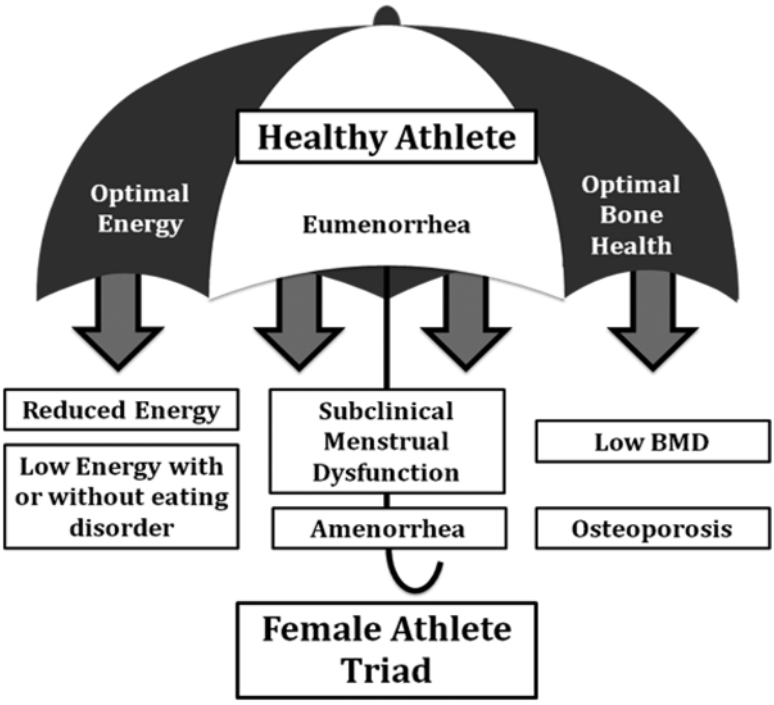

Fig. 10.2 The Female Athlete Triad is now defined as a spectrum disorder, so many female athletes may fit under the umbrella of the Triad without having all three features of the Triad concomitantly

literature reports that disordered eating can affect up to 70 % of athletes compared to 10 % in the general population, that secondary amenorrhea has a 65–69 % prevalence in female ballet dancers, and that there is a 2–4× higher prevalence of low BMD among athletes compared to the general population when disordered eating and amenorrhea is present [2–4, 6, 9, 10, 12]. In contrast, studies done evaluating the Triad under the criteria prior to 2007 report a Triad prevalence of 1.2 % in high school athletes, 2.7 % in collegiate athletes, and 4.3 % in elite athletes [13–15]. Such contrasting numbers suggest that the prevalence of the Triad as defined as a spectrum disorder is likely much higher than previously reported in the literature.

Bone Formation

Epidemiology

BMD Accrual, Sex Differences, and Affected Athletes

Ninety percent of BMD is accrued by adolescence and a net peak in bone mass usually occurs around 26 years of age [16]. Normal females gain approximately 2 % of bone mass per year while amenorrheic females lose 2 % per year. Once females

Table 10.1 There are many medical conditions outside of the Female Athlete Triad that leave patients at a greater risk of reduced BMD. Some examples are highlighted below

Conditions associated with increased risk of low BMD
• Hormone abnormalities (estrogen deficiency, excess parathyroid and thyroid)
• Osteogenesis imperfecta
• Long-term glucocorticoid use
• Long-term anticonvulsant use
• Smoking
• Vitamin D deficiency
• Conditions that require prolonged limb immobilization
• Conditions that prevent nutrient uptake (e.g., Celiac disease and Crohn's disease)

reach their late twenties, they can no longer increase their bone mass—only lose or maintain what they have.

In general, athletes have been found to have a 5–15 % greater BMD level compared to the general population [17]. However, athletes with disordered eating and amenorrhea have shown a 2–4 times higher prevalence of low BMD compared to the general population [6, 12].

Males tend to have higher peak BMD after puberty compared to females [18]. Further, 40 % of women and 25 % of men aged 50 years and older will sustain an osteoporotic fracture. While both sexes will lose BMD over time, females undergo menopause that results in an accelerated bone loss [19].

Among females there are specific sport types that increase a female athlete's risk of developing the Female Athlete Triad and subsequent reduced BMD. Aesthetic/weight-dependent sports, such as figure skating, gymnastics, endurance running, lightweight rowing, cycling, and dance leave athletes at a greater risk since there is often incredible pressure from coaches and peers to maintain a certain weight and physique.

Predispositions to Reduced BMD

There are also certain medical conditions and therapies associated with reduced BMD, including metabolic disorders, such as estrogen deficiency, excess parathyroid and thyroid hormone, osteogenesis imperfecta, long-term glucocorticoid or anticonvulsant use, smoking, vitamin D deficiency, rheumatoid arthritis, and conditions that prevent nutrient uptake, such as Celiac disease (sprue) or Crohn's disease (Table 10.1). Identification of secondary causes of low bone mass is important to potentially reverse or treat the underlying cause of low bone density and osteoporosis.

Stress Fractures from an Orthopaedic Surgeon's Perspective

Stress fractures are the result of bone not being able to handle the stress introduced to it. This is due to both intrinsic and extrinsic factors that result in microdamage to the bones structure and integrity. Intrinsic factors include bone structure and density, vascularity,

metabolism, menstrual cycle, anatomic alignment, endurance, and initial fitness level. Extrinsic factors include nutrition, exercise surface, shoe wear, and changes in training regimen such as increasing the amount of time or intensity of the exercise.

If bone is weak prior to seeing these "stresses," it is at higher risk of having a stress injury. Bone is a living tissue and responds to stress if it is introduced slowly. When bone undergoes too much impact too quickly, it will result in a stress reaction and if the impact persists, the end result will be a stress fracture. Certain stress fractures may be more resistant to healing or more likely to require surgical intervention. These include—navicular, anterior tibia and fifth metatarsal fractures [20].

A detailed patient history can often lead to the diagnosis of a stress fracture. Pain with activity over a few weeks getting progressively worse until unable to continue with activity is a common scenario. Clinical exam demonstrates tenderness over the area of the stress fracture. Radiographs may demonstrate the injury, but an MRI is most sensitive and specific to understanding the extent of bone and soft tissue injury. Once a female athlete presents with a stress fracture—it is paramount that the clinician considers the Female Athlete Triad as a cause.

Most stress fractures will heal with symptomatic treatment—rest the affected bone and allow it to heal. The location of the fracture and the extent of injury dictate the treatment. Most stress fractures will take 3 months to completely heal. Certain fractures and situations in competitive athletes may warrant more aggressive surgical intervention. Other modalities to speed the healing process are available but none have demonstrated any clear advantages—future research is promising. These include—bisphosphonates, teriparatide, pulsed ultrasound, and extracorporeal shock wave therapy. The most important thing to consider when seeing an athlete with a stress fracture is making sure there is not an underlying cause or any other components of the Female Athlete Triad.

Awareness of the Female Athlete Triad

Prior Studies

The first Female Athlete Triad awareness study was published in 2006, which assessed the awareness of athletic trainers, coaches, medical students, physical therapists, and physicians concerning this disorder [21]. According to surveys of 240 health care professionals, only 48 % of physicians and 32 % of medical students were able to identify the Female Athlete Triad and only 9 % of physicians felt comfortable treating a patient with this disorder; only 36 % of pediatricians could identify the Triad components and 4 % were comfortable treating the disorder. This study was limited by sample size and did not assess knowledge of the new Female Athlete Triad definition [22].

Another study subsequently examined the awareness of coaches about the Female Athlete Triad [22]. While about 43 % of coaches properly identified the three components of the Triad, only 8 % of coaches assessed menstrual function prior to sport participation. This study had several limitations, including: a sample size (91 coaches), minimal 30 % response rate, and a predominant response from female coaches, which is not indicative of the demographic of athletic coaches [22].

Current Awareness Study

In a recent study conducted at three prominent academic institutions, awareness of the Triad by physicians was also surprisingly low. Among 931 physicians surveyed, only 37 % had heard about the Triad (Fig. 10.3). Of the physicians surveyed, 51 % felt comfortable treating or referring a patient with the Triad, while 49 % did not. Orthopaedic surgery had the highest level of awareness (80.3 %) and anesthesiology (9 %) had the lowest levels of awareness (Fig. 10.4). On average, only 2.1 out of the

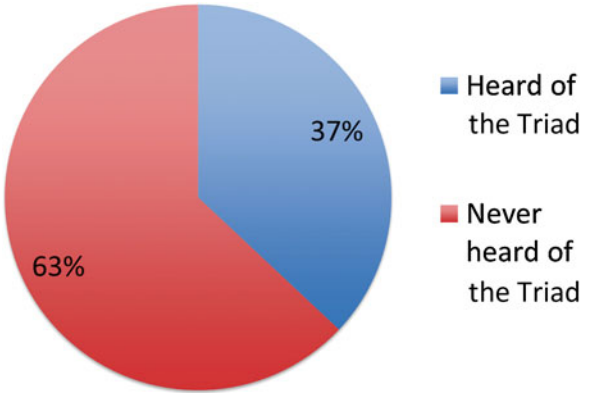

Fig. 10.3 Overall percentage of people who have heard of the Triad compared to those who have not heard of the Triad

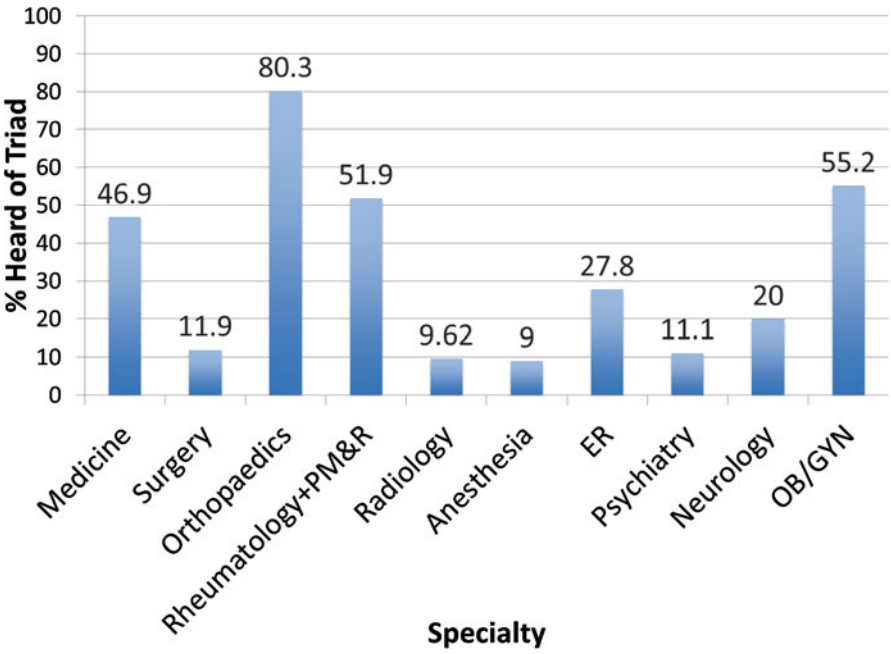

Fig. 10.4 The percentage of respondents that have heard of the Female Athlete Triad based on specialty

three components could be properly identified. This initial study demonstrated that there is a need to educate physicians about the Triad spectrum so that they can diagnose those at risk for this disorder, discuss treatment interventions, and/or refer affected patients to the appropriate health professionals.

Strategies to Promote Identification of Patients with Female Athlete Triad

The best approach to identifying patients who have or who are at risk for developing the Female Athlete Triad centers on obtaining a comprehensive history. In the Orthopaedist's office, this includes taking a proper history of calcium and vitamin D intake, menstruation history and frequency, a history of stress reactions, stress fractures or fractures, exercise habits, and an assessment of energy availability. An open dialogue about the Triad components allows the clinician to gain the pertinent data, while also reviewing the importance of these issues to the patient.

Earlier chapters in this guide detailed these patient history themes; however, it is important to emphasize how incorporation of medical history that focuses on the factors that contribute athlete Triad will promote bone health in the female athlete. A verbal or written screening measure can be used to obtain nutritional, exercise and menstrual history. Multiple screening tools exist and each clinician must determine the best measure for his/her practice [23]. Based on these screening questions, if the athlete is determined to be at risk, further evaluation in all three components of the Triad should be initiated. This investigation should include a multidisciplinary approach, necessitating referral to other specialists.

During the patient evaluation, particular attention should be placed on identifying risk factors and warning signs. There are several nutritional, exercise-based and psychological behaviors known to be associated with increased risk of the Triad, such as participation in lean sports, menstrual irregularities, or stress fractures [24–28]. However, other warning signs may include a history of frequent injuries, mood changes, or a decrease in athletic performance.

As clinicians, we must also remember that components of the Triad occur in women participating in sport at all levels, including recreational and club athletes. We must have a low threshold to delve deeper into an area of concern.

Strategies to Increase Awareness of the Female Athlete Triad

Patient-Based Strategies

Increasing awareness of the Female Athlete Triad ought to be done at the patient and community-based level. Patient-based strategies focus on educating the athlete about the Triad, its components, and its impact on the athlete's body. Miller et al. [29]

found 45 % of female athletes surveyed did not identify a relationship between menstrual dysfunction and poor bone health, highlighting a disconcerting lack of awareness with the Triad. Even more troubling, 22 % of athletes participating in lean sports would not seek treatment for amenorrhea [29].

Several factors, intrinsic and extrinsic, will determine the athlete's nutritional and exercise habits. While the methods employed to increase awareness of the Triad have common themes, an individualized approach with each athlete, noting that each sport also has its own intricacies, should be utilized. Awareness is the first step in changing a behavior. Below, we have highlighted important themes in enhancing Triad awareness at the patient level:

1. Describe the three components of the Female Athlete Triad
2. Emphasize energy availability as an important component of successful training and performance
3. Recommend appropriate training: employ the "10 % Rule" (i.e., never increase your exercise, time, running mileage, or weights by greater than 10 % compared to the previous week)
4. Highlight that menstrual dysfunction is not a normal consequence of participating in sports
5. Inform your athletes about the peak bone-building years of adolescence and young adulthood

Population-Based Strategies

It is paramount to increase Female Athlete Triad awareness by educating the athletic community.

Developing a Multidisciplinary Team

One of the primary risks for the athlete is difficulty in identification. A benefit of the development of a multidisciplinary team is to engage a team of clinicians, coaches, and other professionals in the athletic community and heighten awareness about the Triad and its warning signs. This multipronged approach is preferred for athletes diagnosed with the Female Athlete Triad to ensure proper management of the interrelated components. The optimal team includes many subspecialists, including physicians, nutritionists, coaches, athletic trainers, and mental health professionals. A team-centered approach will maximize the patient's recovery through the development of a comprehensive treatment plan with a strong emphasis on patient education [30].

Female Athlete Triad Screening and Pre-participation Evaluation

The Female Athlete Triad Coalition is an international consortium and consists of several organizations including the American College of Sports Medicine (ACSM), the American Academy of Family Physicians, and International Olympic Committee (IOC). Together, the coalition has developed guidelines for Triad screening [31]. The screening questions include items that evaluate disordered eating, menstrual dysfunction, and the risk of fractures. Questions that correlated with reduced BMD in runners were identified by Barrack et al. [32] in 2008 and are highlighted in the IOC Consensus Statement on Periodic Health Evaluation of Elite Athletes in 2009 (Table 10.2) [33]. These screening points may be integrated in the Pre-Participation Evaluation (PPE) performed prior to the start of sport involvement. The PPE is a convenient and streamlined opportunity to screen athletes (Fig. 10.5) [12, 34]. On the basis of these screening questions, if the athlete is determined to be at risk, further evaluation in all three components of the Triad should be initiated.

Educate the Athletic Community

Clinicians, as they build their multidisciplinary teams, should educate the leaders in the athletic community on the components of the Triad and its impact on the athlete's well-being. Coaches, in particular, have a powerful role and have an opportunity to be a strong influence on their athletes. In addition to identification, the athletic community can help with prevention, including implementing the below tips:

1. Minimize revealing uniforms or sports attire: if an athlete feels exposed or uncomfortable, they may be at risk for disordered eating.
2. Be aware of the pressures placed on your athletes: disordered eating may be employed as a strategy to deal with pressure.
3. Dispel the myth that leanness equates to performance.

1. Have you been consciously trying to restrict the amount of food you eat to influence your shape or weight?
2. Have you gone for long periods of time (8 or more) without eating anything in order to influence your shape or weight?
3. Have you attempted to avoid eating any foods that you like in order to influence your shape or weight?
4. Have you attempted to follow definite rules regarding your eating in order to influence your shape or weight; for example, a calorie limit, a set amount of food, or, rules about what or when you should eat?
5. Have you had a definite desire for your stomach to feel empty?

Table 10.2 Questions highlighted by Barrack et al. in 2008 that correlated with reduced BMD in high school runners and are recommended by the IOC to be used on PPEs

Appendix 1

Athlete PHE Form

MEDICAL HISTORY

Demographic

Personal Information

Last Name _____ First Name _____
Address: Street _____ City_____ Region_____
Post Code_____ Country_____
Preferred Language: _____
Birthdate: yyyy_____/mm_____/dd_____
Sex (M/F):_____
Phone: Home_____ Mobile_____
Emergency Contact 1: Name_____ Relationship _____ Phone _____
Emergency Contact 2: Name_____ Relationship _____ Phone _____
Health Care Insurance (company number): _____
Family Physician (name, phone number): _____

Background

The following questions ask for information regarding your personal background

What is your main sport? (sport, event/position): _____

Have you participated in other sports in the past (include those sports you have done competitively)? No❑ Yes ❑: _____
What is your ethnic origin?: _____

Do you have any religious convictions that could affect your medical treatment?	No ❑	Yes ❑
When was the last time you had a complete physical examination?: _____		
Have you ever failed a pre-participation examination for sports, or has your doctor ever stopped you from participating in sports for any reason?	No ❑	Yes ❑

In total, how many days have you missed practice or competition in the past year because of injury or illness?: _____

Heart

Have you ever had any of the following heart or circulation related problems?:

Chest pain, discomfort, tightness or pressure with exercise?	No ❑	Yes ❑
Unexplained fainting or near fainting or passed out for no reason DURING or AFTER exercise?	No ❑	Yes ❑
Excessive or unexplained shortness of breath, lightheaded, or fatigue with exercise?	No ❑	Yes ❑
Do you get more tired or short of breath more quickly than your friends during exercise?	No ❑	Yes ❑
Does your heart race or skip beats (irregular beats) during exercise?	No ❑	Yes ❑
Heart murmur, high blood pressure, high cholesterol, heart infection or inflammation, rheumatic fever, heart valve problems, or any other heart related problem?	No ❑	Yes ❑
Have you ever had an unexplained seizure?	No ❑	Yes ❑
Any tests for your heart (for example, ECG or EKG, echocardiogram)?	No ❑	Yes ❑

Breathing

Have you ever had any of the following respiratory or breathing problems:

Do you have asthma?	No ❑	Yes ❑
Do you have any other symptoms of respiratory (lung) disease including, wheezing, cough, postnasal drip, hay fever, or repeated flu like illness?	No ❑	Yes ❑
Do you cough, wheeze or have more difficulty breathing than you should during or after exercise?	No ❑	Yes ❑
Have you ever used asthma medication (such as an inhaler)?	No ❑	Yes ❑
Have you ever had bronchitis, pneumonia, tuberculosis, cystic fibrosis or other respiratory or other breathing problem?	No ❑	Yes ❑

Heat

The following questions are about exercise in the heat:

Have you ever become ill while exercising in the heat?	No ❑	Yes ❑
Have you ever been diagnosed with heat exhaustion, heat stroke or hyperthermia?	No ❑	Yes ❑
Do you get frequent muscle cramps while exercising?	No ❑	Yes ❑
Have you ever had electrolyte (salt) or fluid imbalance?	No ❑	Yes ❑

Medical

Do you have any ongoing medical conditions or illness?	No ❑	Yes ❑
Do you have, or have you ever had any symptoms of medical problems such as:		
Infections mononucleosis (**mono**), flu like symptoms or viral illness within the past month?	No ❑	Yes ❑
Disease of the **ears** (infections, hearing loss, pain), **nose** (sneezing, itchy nose, sinusitis, blocked nose) or **throat** (sore throat, hoarse voice, swollen glands in the neck)?	No ❑	Yes ❑
Blood disorders such as anemia, low iron stores, sickle cell trait or sickle cell disease, abnormal bleeding or clotting disorder, blood clot (embolus), or other blood disorder?	No ❑	Yes ❑
Immune system including current infections, recurrent infections, HIV/AIDS, leukemia, or are you using any immunosuppressive medication?	No ❑	Yes ❑
Skin problems such as rashes, infections (fungus, herpes, MRSA) or other skin problems?	No ❑	Yes ❑
Kidney or bladder disease, blood in the urine, loin pain, kidney stones, frequent urination, or burning during urination?	No ❑	Yes ❑
Gastrointestinal disease including heartburn, nausea, vomiting, abdominal pain, weight loss or gain (> 5kg), a change in bowel habits, chronic diarrhea, blood in the stools, or past history of liver, pancreatic or gallbladder disease?	No ❑	Yes ❑
Nervous system including past history of stroke or transient ischaemic attack (TIA), frequent or severe headaches, dizziness, blackouts, epilepsy, depression, anxiety attacks, muscle weakness, nerve tingling, loss of sensation, muscle cramps, or chronic fatigue?	No ❑	Yes ❑
Metabolic or hormonal disease including diabetes mellitus, thyroid gland disorders, or hypoglycemia (low blood sugar)?	No ❑	Yes ❑
Infections such as meningitis, hepatitis (jaundice), or chicken pox?	No ❑	Yes ❑
Arthritis or joint pain, swelling and redness not related to injury?	No ❑	Yes ❑
Were you born without, or are you **missing** a kidney, an eye or any other organ?	No ❑	Yes ❑

Fig. 10.5 (**a–e**) Pre-participation evaluation form recommended by the International Olympic Committee (IOC) from the IOC Consensus Statement from 2009. [Courtesy of the International Olympic Committee (IOC)]

An **injury** to the any internal organs such as your liver, spleen, kidney(s) or lung? No ❑ Yes ❑
Have you ever had **surgery**? (explain) No ❑ Yes ❑
Do you get motion sickness (car, air or sea sickness)? No ❑ Yes ❑
Do you have any other medical problems? No ❑ Yes ❑

Family

Do any of your family members have a history of any of the following conditions (in male relatives < 55 years, female relatives < 65 years):

Sudden death for no apparent reason (including drowning, unexplained car accident, or sudden infant death syndrome)? No ❑ Yes ❑
Unexplained fainting, seizures, or near drowning? No ❑ Yes ❑
Died before age 50 due to heart disease? No ❑ Yes ❑
Disability or symptoms from heart disease before age 50? No ❑ Yes ❑
Other heart problems including electrical problems (arrhythmia) or heart enlargement, cardiomyopathy, heart surgery, pacemaker or defibulator? No ❑ Yes ❑
High blood pressure or high blood cholesterol? No ❑ Yes ❑
Marfan's Syndrome? No ❑ Yes ❑
Bleeding disorder, Sickle cell trait or sickle cell disease? No ❑ Yes ❑
Tuberculosis or Hepatitis? No ❑ Yes ❑
Anaesthetic reaction or problem? No ❑ Yes ❑
Other condition such as stroke, diabetes, cancer, arthritis (describe)? No ❑ Yes ❑
Are you unsure of your family history? No ❑ Yes ❑

Medications

The following questions are about medications and supplements you are taking, or have taken in the past month:

Medications that have been prescribed by a doctor (include insulin, allergy shots or pills, sleeping pills, anti-inflammatory medications etc.)? No ❑ Yes ❑
Non-prescription medications (include pain killers, anti-inflammatories, etc.)? No ❑ Yes ❑
Vitamin or mineral **supplements** or herbal medicines? No ❑ Yes ❑
Other substance to improve your athletic performance (include substances like creatine, weight gain products, amino acids, etc.)? No ❑ Yes ❑
Have you ever been offered or encouraged to use **banned performance enhancing drugs**? No ❑ Yes ❑

Allergies

Do you have any allergies to:

Medication? No ❑ Yes ❑
Anything else, such as foods, pollens, stinging insects, any plant material or any animal material? No ❑ Yes ❑

Immunization

Indicate which immunizations you have received:

Tetanus / Diptheria (Td or Tdap)? No❑ Yes ❑: Last shot? _____
Measles / Mumps / Rubella (2 shots)? No❑ Yes ❑
Chicken Pox (Varicella)? No❑ Yes ❑
Meningitis (Menimune or Menactra)? No❑ Yes ❑
Hepatitis A (2 shots)? No❑ Yes ❑
Hepatitis B (3 shots)? No❑ Yes ❑
Malaria? No❑ Yes ❑
Have you had a TB Test (PPD)? No❑ Yes ❑ Result? _____
Have you had any other immunizations? No❑ Yes ❑ Explain: _____

Female

These questions are for females only:

Have you ever had a menstrual period? No ❑ Yes ❑
What was your age at your first menstrual period?: _____
Do you have regular menstrual cycles? No ❑ Yes ❑
How many menstrual cycles did you have in the last year?: _____
When was your most recent menstrual period?: _____
Have you had a stress fracture in the past? No ❑ Yes ❑
Have you ever been identified as having a problem with your bones such as low bone density (osteopenia or osteoporosis)? No ❑ Yes ❑
Are you presently taking any female hormones (estrogen, progesterone, birth control pills)? No ❑ Yes ❑
Have you ever had a sexually transmitted disease such as gonorrhea, syphilis, venereal warts, chlamydia or other infection? No ❑ Yes ❑

Male

These questions are for males only:

Do you have two normal testicles? No ❑ Yes ❑
Have you ever had a hernia or swelling around the testicle (varicocele, hydrocele)? No ❑ Yes ❑
Have you ever had an injury to a testicle? No ❑ Yes ❑
Have you ever had surgery for an undescended testicle, testicular injury or problem? No ❑ Yes ❑
Have you ever had a sexually transmitted disease such as gonorrhea, syphilis, venereal warts, chlamydia or other infection? No ❑ Yes ❑

Head & Neck

Have you ever had any of the following problems related to your head or neck?:

Eye injury, or other problems with your vision? No ❑ Yes ❑
Headaches with exercise? No ❑ Yes ❑
Have you ever had numbness, tingling or weakness in your arms and legs or been unable to move your arms or legs after being hit or falling? No ❑ Yes ❑
Do you have, or have you been x-rayed for, neck (atlantoaxial) instability? No ❑ Yes ❑
Have you had an injury to your teeth? No ❑ Yes ❑
Do you have any other decayed, missing or filled teeth? No ❑ Yes ❑
Do you have a dental prosthesis or appliance? No ❑ Yes ❑
Have you had your wisdom teeth removed? No ❑ Yes ❑

Injury

Have you ever had an injury to your face, head, skull or brain (including a concussion, confusion, memory loss or

Fig. 10.5 (continued)

headache from a hit to your head, having your "bell rung" or getting "dinged")?	No ❑	Yes ❑
Have you had a problem or an injury like a sprain, strain, muscle or ligament tear, or tendonitis, broken bone, stress fracture or joint injury (that caused you to miss a practice or competition) to any of the following areas of your body?		
Neck or spine (including a "stinger," or "whiplash,")	No ❑	Yes ❑
Upper back (thoracic spine)	No ❑	Yes ❑
Lower back (lumbar spine)	No ❑	Yes ❑
Chest and ribs	No ❑	Yes ❑
Shoulder area (including collar bone)	No ❑	Yes ❑
Upper arm	No ❑	Yes ❑
Elbow	No ❑	Yes ❑
Lower arm (forearm)	No ❑	Yes ❑
Wrist	No ❑	Yes ❑
Hand or fingers	No ❑	Yes ❑
Pelvis, groin or hip (including sports hernia)	No ❑	Yes ❑
Thigh (including hamstrings and quadriceps)	No ❑	Yes ❑
Knee	No ❑	Yes ❑
Lower leg (calf or shin)	No ❑	Yes ❑
Ankle	No ❑	Yes ❑
Foot, heel or toes	No ❑	Yes ❑
Other		
Tests - If not already mentioned above, have you had any other tests, for any injury or condition including blood tests, X-rays, MRI, CT scan, Bone scan, Ultrasound,Electroencephalogram (EEG), Electromyogram (EMG), Nerve conduction studies (NCS), Electrocardiogram (ECG/EKG), Echocardiogram (Echo), Exercise stress test or other tests?	No ❑	Yes ❑
Treatment - If not already mentioned above, have you ever received any of the following treatments for any condition?		
Surgery?	No ❑	Yes ❑
Been prescribed a **brace, sling, cast, walking boot, orthotic**, **crutches** or other appliance?	No ❑	Yes ❑
Cortisone injection?	No ❑	Yes ❑
Been prescribed other **rehabilitation or therapy**?	No ❑	Yes ❑
Have you ever spent the night **in a hospital** or been admitted to a hospital as an inpatient or outpatient?	No ❑	Yes ❑
Been referred to a **medical specialist** (cardiologist, neurologist or other medical person) for any condition not already mentioned?	No ❑	Yes ❑
Equipment		
Do you wear eye glasses or contact lenses?	No ❑	Yes ❑
Are you **currently** using any of the following protective equipment?	No ❑	Yes ❑
Do you use protective eyewear?	No ❑	Yes ❑
Special equipment (pads, braces, etc.)?	No ❑	Yes ❑
Mouth guard for sports?	No ❑	Yes ❑
If you wear a **helmet** for sports, how old is it?	No ❑	Yes ❑
Nutrition		
The following questions are about nutrition:		
Do you worry about your weight or body composition?	No ❑	Yes ❑
Are you satisfied with your eating pattern?	No ❑	Yes ❑
Are you a vegetarian?	No ❑	Yes ❑
Do you lose weight to meet weight requirements for your sport?	No ❑	Yes ❑
Does your weight affect the way that you feel about yourself?	No ❑	Yes ❑
Do you worry that you have lost control over how much you eat?	No ❑	Yes ❑
Do you make yourself sick when you are uncomfortably full?	No ❑	Yes ❑
Do you ever eat in secret?	No ❑	Yes ❑
Do you currently suffer or have you ever suffered in the past with an eating disorder?	No ❑	Yes ❑
What is your current weight? ___	No ❑	Yes ❑
How tall are you without shoes? ___	No ❑	Yes ❑
Discuss		
Do you have any other concerns that you would like to discuss with a doctor?	No ❑	Yes ❑

Explain "YES" answers here:

I hereby state that, to the best of my knowledge, my answers to the above questions are complete and correct.

Signature of athlete: _____

Signature of parents or legal representative (when needed): _____ Date _____

Fig. 10.5 (continued)

PHYSICAL EXAMINATION

Date of Examination:_____

Medical	NORMAL	ABNORMAL (specify)
Appearance		
Eyes/ears/nose/throat		
Hearing		
Lympth nodes		
Heart		
Rhythm		
Heart sounds / murmurs in supine and standing		
Peripheral oedema		
Physical stigmata of Marfan's syndrome		
Blood vessels		
Peripheral pulses		
Delay in femoral pulses		
Vascular bruits (femoral)		
Varicose veins		
Blood Pressure in Sitting Position (after 5 minutes rest)		
Right arm		
Left arm		
Heart rate (after 5 Minutes rest)		
Lungs		
Abdomen		
Genitourinary (males only)		
Skin		
Eyes		
visual acuity (corrected/uncorrected)		
equal pupils		

Dental

DMF Index = Number of decayed, missing or filled teeth :_____

Oral Hygeine assessment: ❑ Good ❑ Fair ❑ Poor

Visible Oral Infection: ❑ No ❑ Yes

Presence of Worn, Broken or Loose/Mobile teeth: ❑ No ❑ Yes

Dental appliances (bridge, plate, braces or orthodontic appliance): ❑ No ❑ Yes

Musculoskeletal		
Neck		
Back		
Shoulder/arm		
Elbow/forearm		
Wrist/hand/fingers		
Hip/thigh		
Knee		

Fig. 10.5 (continued)

Leg/ankle		
Foot/toes		

Investigations

12 Lead ECG

- ❑ Normal / no changes
- ❑ Common and training-related ECG changes
- ❑ UnCommon training-unrelated ECG changes

Details:

Blood Tests

	Other:
Haemoglobin	
Haematocrit	
Erythrocytes	
Thrombocytes	
Leukocytes	
Ferritin	
Sodium	
Potassium	
Creatinine	
Cholesterol (total)	
LDL Cholesterol	
HDL Cholesterol	
Triglycerides	
Glucose	
C-reactive Protein	

Clinical Evaluation Outcome

The athlete does not present apparent clinical contraindications to practice the following sport(s)

1 (specify): No • Yes •

If the answer to question 1 is "No", it is recommended that the athlete:

avoids participating:

- in training (explain) No • Yes •

- in competition (explain) No • Yes •

respects the following restrictions:

- during training (specify) No • Yes •

- during competition (specify) No • Yes •

undergoes further examinations (specify):

Examining physician

Name: _____ Phone Number: _____

Address: _____ Email _____

Fig. 10.5 (continued)

4. Incorporate performance enhancement techniques which employ mental skills training.
5. Build a network of professionals for consultation when you are concerned about an athlete.
6. Inadequate macronutrients can be detrimental to the body's ability to build bone, maintain muscle mass, and recover from injury [35].

Participate in Female Athlete Triad Research and Medical Education

It is known that health care professionals have a low awareness of the Female Athlete Triad and its components; when surveyed less than half of physicians and physical therapist could identify Triad components [21]. It is paramount to educate the medical community about the Female Athlete Triad. Efforts should be made to integrate the Triad into medical school curriculums and residency education programs. Further awareness can be raised by conducting and publishing research on this matter.

Resources

Recommended Websites

Academy for Eating Disorders (AED): www.aedweb.org
American College of Sports Medicine (ACSM): www.acsm.org
American Dietetic Association (ADA): www.eatright.org
Female Athlete Triad Coalition: www.femaleathletetriad.org
International Olympic Committee Position Stand on the National Association of Anorexia Nervosa and Associated Disorders (ANAD): www.anad.org
National Collegiate Athletic Association (NCAA) Web site on Nutrition and Performance: www.ncaa.org/nutritionandperformance

Recommended Books

Beals K. Disordered eating among athletes. Champaign, IL: Human Kinetics.
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Chapter 11
Future Directions and Research Agenda

Catherine M. Gordon and Meryl S. LeBoff

In this concluding chapter, we would like to reflect on what has been written and assembled in this clinical guide and future research directions. Since passage of the Title IX legislation in 1972, more and more young women engage in physical activity and competitive sports. This opportunity and trend for girls and women to become more athletic has been positive overall, yet has also been accompanied by negative health outcomes for young women. While we have made advances in this area, there remain many gaps in knowledge that drive a future research agenda. We hope to summarize and reflect on important topics for future research.

Recently, the International Olympic Committee (IOC) convened an expert panel to update their consensus statement on the Female Athlete Triad [1]. The IOC working group introduced a broader, more comprehensive term as part of their 2014 statement and endorsed the new term, "Relative Energy Deficiency in Sport" (RED-S) over the previous terminology, "Female Athlete Triad." They recognized the complexity involved in arriving at the most appropriate terminology and fact that male athletes are also affected. RED-S refers to impaired physiological functioning, which may include alterations in metabolic rate, menstrual function, hormonal changes, bone health, immunity, protein synthesis, and cardiovascular health caused by a relative energy

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deficiency. The primary aim of the IOC is to protect the health of athletes. Thus, the expansion of this term is deemed to align with the Committee's primary mission. Research will be needed to define the prevalence/incidences of RED-S compared with the traditional components of the more well-known term, Female Athlete Triad. It will also be important to consider both distinctions and similarities between the two. As has occurred for reports pertaining to the Triad, significant variability can result among studies as differing definitions may be used (e.g., menstrual disorders, disordered eating, osteoporosis). Thus it can be difficult to draw conclusions in this area as different investigative groups may consider varying outcomes. Estimating the prevalence using either terminology with reasonable validity and precision becomes extraordinarily difficult because of the varying ways in which the Triad and its components have been conceptualized and operationalized over many years. This classification will remain a challenge for clinicians and researchers in the years to come.

Considering each chapter in our book, our authors have provided important insights in formulating a future research agenda. Examples include:

- When considering energy availability in an adolescent or adult, adjust for fat-free mass, use an objective method for the assessment, as well as a validated method of assessing dietary intake and energy expenditure, measuring multiple days and accounting for energy expended at rest, non-training physical activity, and athletic training.
- Consideration of the menstrual cycle is critically important in female athletes. The assessment should be comprehensive and include, at a minimum, age at menarche, menstrual function (including over the previous 3 months), and hormonal contraceptive use, with estimates stratified by its use.
- Bone mineral density (BMD) should be considered in those patients with amenorrhea or other documented threats to bone health. The evaluation should include a DXA measurement, reporting *Z*-scores relative to age- and sex-specific standards and avoid *T*-scores. More data are needed on peak bone mass in active children and adolescents, including former and current athletes. Future investigations would benefit from use of 3D imaging technology to assess the bone structural and microarchitectural adaptations that underpin exercise-related gains in bone strength. Shifting the focus away from solely bone mass and towards bone strength will ultimately advance our understanding of skeletal health in this population, and aid in the development of effective treatment and prevention programs.
- There is a need to identify better predictors of stress fractures beyond current measurement tools such as DXA. Importantly for all athletes, there is a need to recognize preventative strategies to ward off these overuse injuries, and to identify effective treatment for those patients with delayed, nonunion or recurrent fractures. Currently, a pilot study among premenopausal women demonstrated a positive anabolic effect with treatment of teriparatide versus placebo, which shows promise for improving stress fracture healing; more data from larger randomized, controlled studies of safe approaches to hasten stress fracture healing are needed. For prevalence reports, the age, sport, and competitive level of the population should be specified, with the sport or group of sports classified as weight sensitive or not weight sensitive, as appropriate.

- Sample sizes should be sufficiently large to produce reasonably precise prevalence estimates for rare outcomes that may arise from these studies, with confidence intervals around all estimates reported.
- Determination of prevalence estimates for physiological counterparts in male athletes will be critical for informing strategies for prevention and monitoring population level changes in risk over time.
- Little is known about prognostic factors and outcomes among patients with bulimia nervosa and binge-eating disorder. This information will advance the field for those who care for these patients.
- Long-term outcome data are needed for young women and men with restrictive eating disorders, including consequences of hormonal abnormalities/bone loss and teens with AN, and implications for peak bone mass and future risk of osteoporosis. Future implications of other medical complications such as brain abnormalities (e.g., gray and white matter changes), abnormal lipid panels, and liver and cardiovascular function. Further study is needed in well-defined groups of varying pubertal stages to pinpoint the window during which the growing skeleton is most responsive to exercise-induced weight-bearing. There is also a need to elucidate the optimal exercise prescription for bone strength. This goal can only be achieved through well-designed, randomized controlled trials that account for confounding factors such as sex and pubertal stage. Considering multiple health end points, the ideal activity regimen for young adults merits further study, acknowledging that which is ideal for the young adolescent with open epiphyses may not be for older adolescents.
- Long-term follow-up of athletes with the Triad would help to clarify the most effective remedial approach for bone health; long-term health outcomes including fracture data are critically needed.
- Treatment with individual hormonal therapies has yet to demonstrate a large, sustainable, positive impact on menstrual function or BMD. Thus, it is paramount that efforts continue to investigate how the various hormonal changes, and exercise activity itself, can enhance, rather than hinder the reproductive system and skeleton in order to prevent Female Athlete Triad and optimize its treatment.

We envision that the research agenda we have summarized, incorporating ideas from each of our authors, will take us into the next decade. Research funding devoted to these questions will lead to improved health for adolescents, young women as well as the older women they "grow up" to be. Of concern are unrecognized health problems from estrogen deficiency among the other hormonal abnormalities that we have discussed. Thus, research efforts devoted to this topic have the potential to improve multiple aspects of health across the lifespan.

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